South African National Department of Health
Rapid Review Report
Component: COVID-19

TITLE: A REVIEW OF THE OPTIMAL DOSE OF EITHER UNFRACTIONATED HEPARIN OR LOW MOLECULAR WEIGHT HEPARIN IN THE PREVENTION OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH SEVERE COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 30 July 2021 *(second update of the initial 19 June 2020 rapid review)*

Key findings

- The correct dose for anticoagulation of patients hospitalised with COVID-19 remains controversial. New trials have recently been reported and this has driven the rapid review update on this topic.
- This review evaluates and reports the safety and efficacy of higher intensity doses of heparin (including unfractionated heparin and low molecular weight heparin) as thromboprophylaxis in hospitalised patients with COVID-19.
- The search was up-to-date as on 16 June 2021 and identified six trials, two evaluated intermediate intensity dosing (severe/ critically ill patients) and four report on therapeutic intensity dosing (mixed hospitalized population).
- For intermediate dosing in severely ill COVID-19 confirmed hospitalized patients: there may be little or no difference to the outcomes death, and there is substantial uncertainty regarding the effect of higher dosing on arterial or venous thrombosis and major bleeding or serious adverse events(low or very low certainty evidence due to low event rates and some risk of bias in the included trials)..
- For therapeutic dosing: There may be little or no difference in mortality or the WHO progression score to level 7 or above between those on intermediate compared to standard dose prophylactic anticoagulation. There may be fewer major thromboembolic events and increased major bleeding events (low certainty due to low event rates and imprecision and some risk of bias in reporting in the trials).
- Overall, on consideration of the balance of benefits and harms, the use of higher doses on anticoagulation (intermediate or therapeutic dosing regimens) does not outweigh the benefits of the current standard of care and use of prophylactics doses on anticoagulation for hospitalized patients with COVID-19.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Based on this evidence review, the NEMLC Subcommittee suggests to use prophylactic doses over intermediate- or therapeutic intensity doses in hospitalised immobilized patients meeting the criteria for prevention of thrombosis.
Rationale: The balance of benefits and harms supports the use of prophylactic rather than therapeutic doses, unless specifically indicated for the management of thrombosis.
Level of Evidence: Low certainty

(Refer to appendix 4 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair).

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

Severe COVID-19 may induce a hypercoagulable state[1-5], although the pathogenesis is poorly understood. Furthermore, coagulopathy secondary to coronavirus infection is associated with a higher mortality [4, 6]. Several coagulation abnormalities have been observed in patients with COVID-19 including increased D-dimer (a degradation product of cross-linked fibrin indicating augmented thrombin generation and fibrin dissolution by plasmin), increased fibrin and fibrin degradation product (FDP), longer prothrombin time and longer activated partial thromboplastin time. These derangements are associated with poor outcome. [4, 6-8] Elevated D-dimer has been the most consistent prognosticator of a poor outcome [10, 11].

Clinical guidelines recommend that all hospitalised patients with COVID-19 receive thromboprophylaxis with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). [12-15] (see Appendix 1). However, the risk of venous thromboembolism (VTE) remains high despite heparin prophylaxis. VTE has been observed in up to one-third of COVID-19 patients in intensive care units, even when prophylactic anticoagulation was used [1, 16]. It has been suggested that higher heparin doses i.e. doses of intermediate or therapeutic intensity may be used to prevent thromboembolism [1, 11, 15-17]. This is despite observations in two retrospective case series wherein the risk of VTE in ICU patients remained despite the use of of higher doses of LMWH [8, 17]. Consequently, neither the optimal dosing nor clinical benefit of heparin prophylaxis in patients with severe COVID-19 are known[11]. We review evidence to date that may inform recommendations regarding the dosing of heparin to prevent VTE in severe COVID-19 patients in South Africa.

A recent systematic review on the incidence of thromboembolism in patients with COVID-19 and whether antithrombotic therapies improve outcomes[18], found that, overall, there are a small number of applicable studies each with serious methodological limitations or inadequate reporting relating to the incidence of thromboembolic events in acutely and critically ill hospitalized patients. Evidence regarding dosing of heparin or LMWH was equally weak. Different approaches have been suggested in the past year, including standard thromboprophylaxis dosing or regimen with higher than standard dosing, so called intermediate dosing or therapeutic dosing regimens. Increasingly trials in patients hospitalised with mild/ moderate or severe/ critical COVID-19 are being reported in publications or pre-prints which can inform our recommendations for thromboprophylaxis dosing for hospitalised patients in South Africa.

RESEARCH QUESTION:

What is the optimal heparin dose (intermediate or therapeutic dose regimens) for the prevention of venous thromboembolism in patients hospitalised with severe COVID-19, including those with (critically ill) and without (acutely ill) requirement for oxygen therapy/ ventilatory assistance?

METHODS

This is the second update of a rapid review conducted first in June 2020, updated in September 2020. The original evidence search involved systematic searching of four electronic databases (PubMed as well as the Epistemonikos, Cochrane COVID Study Register and L-OVE Working Group databases). For the last update update, the search included the Epistemonikos (https://app.iloveevidence.com/ in the COVID-19 evidence platform) and Cochrane's COVID-19 study register (https://covid-19.cochrane.org/) and was searched until August 2020.
For this update we searched Epistemonikos (https://app.iloveevidence.com/ in the COVID-19 evidence platform) and Cochrane's COVID-19 study register (https://covid-19.cochrane.org/) on 22 April 2021, with a date restriction in Cochranes COVID-19 register from 1 August 2020 to 22 April 2021. All results from this recent search were uploaded into Covidence, a reference management software for reviews. In addition, the www.covid-nma living systematic review site was searched for trials until 16 June 2021. Search details are reported in appendix 2 table C.
Additionally we searched for updates on the following guidelines: World Health Organization (WHO), Australian guidelines, American Society of Hematology and National Institute of Health (NIH, USA).

Records were screened in duplicate (NB, FB, LF, TK). Data was extracted by one reviewer (NB or VN) and checked by a second reviewer and the author team. Data extraction included study details, participants and intervention and comparison details and assessment of risk of bias was extracted from the living systematic review, www.covid-

nma.com. Where meta-analaysis was not available on covid-nma, a random effects meta-analysis was conducted using Revman software. Trial details are provided in the table of included studies (see Table 1).

Eligibility criteria for review

Population: Hospitalised patients with confirmed or suspected COVID-19 receiving either UFH or LMWH as thromboprophylaxis. No restriction on age.

Intervention: Dosing higher than prophylactic doses of either unfractionated or low molecular weight heparin used as thromboprophylaxis.

Comparators: Prophylactic doses of either unfractionated or low molecular weight heparin.

Outcomes:

1. Mortality
2. Thromboembolic events
3. Duration of hospitalisation
4. Progression to ICU admission
5. Progression to mechanical ventilation
6. Duration of ICU stay
7. Duration of mechanical ventilation
8. Adverse reactions and adverse events: e.g. major bleeding events

Study designs: randomised controlled trials, and systematic reviews of trials.

RESULTS

Search results

We conducted our search on 22 April 2021 and searched the www.covid-nma.com site until 16 June 2021. We identified 507 unique records after removing 36 duplicates. We identified no recent systematic reviews with trial data. From the database searches, we identified two eligible randomised trials, INSPIRATION trial (Bikdeli et al)[19] and Zarychanski et al[20] (from the REMAP-CAP, ACTIV-4A, ATACC investigators). We identified additional four trials, Perepu et al[21], HESACOVID (Lemos et al)[22] , Lawler et al[23] (from the ATTACC, ACTIV-4a, and REMAP-CAP Investigators) and ACTION (Lopes et al)[24] by searching the www.covid-nma.com living review website. Guideline updates were available for WHO, NIH and Australian COVID-19 task force guidelines.

Description of the studies

Table 1 reports the main characteristics and outcomes of the included studies

We identified six trials for inclusion.
The studies may be separately considered in two comparisons: comparison 1 – *intermediate dose anticoagulation compared to standard prophylactic dose anticoagulation* including two trials, Inspiration (Bikdeli et al) trial[19] and Perepu et al[21] and comparison 2 – *therapeutic dose anticoagulation compared to standard prophylactic dose anticoagulation* HESACOVID (Lemos et al)[22], Zarychanski et al [20](note this trial is labeled Goligher et al in the forest plots), Lawler et al[23], and Lopes et al[24]

The populations differ and sub-groups are reported in the results accordingly: 1) severe/ critically ill (requiring respiratory or cardiovascular organ support – i.e. high flow nasal cannula, non-invasive ventilation, invasive ventilation, vasopressors, or inotropes)) or 2) mildly/ moderately ill not requiring organ support.

Comparison 1 Intermediate dose anticoagulation compared to standard prophylactic dose anticoagulation

- *Severe/critically ill*

The Inspiration trial is a published multicenter trial in Iran with follow up of 90 days. Trialists randomized adult patients (n = 598, 299 in each group) with PCR-confirmed severe COVID-19 admitted to ICU within 7 days of initial hospitalization with no other specific indication for anticoagulation. Intervention dose: enoxaparin, 1mg/kg daily vs standard prophylactic dose: enoxaparin, 40mg daily.

Risk of bias was assessed as having some concerns due to possible retrospective selecting of outcomes that were reported. Blinding of outcome assessors was done but not participants or personnel. It is probably low risk of bias for the outcomes clinical improvement, WHO score 7 and above and serious adverse events.

The Perepu et al trial (pre-print) is a multicenter open label trial in USA with follow up of 30 days. Eligible patients over 18 years were included (n = 176, 88 in each group) with PCR-confirmed COVID-19 requiring hospitalization and admitted to an ICU and/ or had modified ISTH overt DIC score >= 3 without indication for anticoagulation. Intervention dose: enoxaparin 1 mg/kg SC daily if the BMI was < 30 or 0.5 mg/kg SC twice daily if the BMI was ≥ 30; standard dose: enoxaparin 40 mg SC daily if the body-mass index (BMI) was less than 30 kg/m2 and 30 mg SC twice daily for non-ICU patients or 40 mg SC twice daily for ICU patients if the BMI was ≥ 30. Primary outcome was all cause mortality, with thromboembolism and major bleeding secondary outcomes.
Risk of bias assessment suggested some concerns due to analysis of outcomes mortality and time to death. This is a pre-print awaiting peer review and publication.

Comparison 2 Therapeutic dose anticoagulation compared to standard prophylactic dose anticoagulation

- *Severe/ critical ill population requiring mechanical ventilation and/ or organ support*

Zachyranski et al (REMAP-CAP, ACTIV-4A, ATACC) is an open label, adaptive, multiplatform, randomized trial (pre-print). Eligible patients had severe COVID-19 (requiring respiratory or cardiovascular organ support – i.e. high flow nasal cannula, non-invasive ventilation, invasive ventilation, vasopressors, or inotropes) (n = 1,074 participants (529 in intervention, 545 thromboprophylaxis). Dosing was site dependent, most participants received enoxaparin or dalteparin (>70%) - Intervention dose: therapeutic anticoagulation (from available data n = 443, 77.7% received therapeutic dose anticoagulation, 10.9% received intermediate dose, 7.7% received subtherapeutic dose, and 3.6% received low dose thromboprophylaxis; comparison dose: usual care thromboprophylaxis (from available data, n = 465, 51.3% received intermediate dose thromboprophylaxis, 41.3% received low dose thromboprophylaxis and 7.4% received therapeutic or sub-therapeutic anticoagulation (see supplemental table from the trial S1). Recruitment took place from April 2020 and early termination in December 2020 for futility. The primary outcome was an ordinal scale combining in-hospital mortality (assigned –1) and days free of organ support to day 21.
Risk of bias has some concerns due to deviation form interventions for the outcome's mortality and clinical improvement.

Lemos et al is a randomized open label phase II study including patients > 18 years with PCR-confirmed COVID-19 patients (n = 20, 10 in each group) requiring mechanical ventilation. Intervention dose: enoxaparin 1 mg/Kg BID adjusted for renal function as required, vs standard dose: subcutaneous unfractionated heparin (UFH) 5000 IU TID (if weight < 120 kg) and 7500 IU TID (if weight > 120 kg) or enoxaparin at a dose of 40 mg OD (if weight < 120 kg) and 40 mg BID (if weight > 120 Kg). The trial primary outcome was the variation in gas exchange over time evaluated through the ratio of partial pressure of arterial oxygen (PaO2) to the fraction of inspired oxygen (FiO2) at baseline, 7, and 14 days after randomization, safety outcomes included bleeding.
Risk of bias has some concerns for the outcome mortality, allocation concealment is not clearly reported and the registration of the trial plan was done retrospectively suggesting possible selective outcome reporting.

- *Mild/ moderately ill population hospitalized*

Lawler et al (REMAP-CAP, ACTIV-4A, ATACC) is an open label, adaptive, multiplatform, randomized trial (pre-print). Participants (2245 were randomized, but trial stopped after analysis of 1398 participants) were within 72hrs of hospitalisation with PCR-confirmed COVID-19 with mild/ moderate illness not requiring organ support. Intervention dose: therapeutic anticoagulation e.g. enoxaparin 1mg/kg subcutaneous twice daily (from available data n = 1043, 79.6% received therapeutic dose anticoagulation, 8.7% received subtherapeutic dose 5.8% received intermediate dose, and 5.8% received low dose thromboprophylaxis; comparison dose: thromboprophylaxis e.g. enoxaparin 40mg sc daily or another allowed medicine (see supplement in trial S1, table S3). (from available data, n = 855, 71.7% received low dose thromboprophylaxis, 26.5% received intermediate dose thromboprophylaxis and <1% received therapeutic or sub-therapeutic anticoagulation (see supplemental table S3)

Mixed population (mild, moderate, severe and critical)
Lopes et al was a multicentre open label trial in Brazil. It ran from June 2020 to February 2021 and included 615 participants (intervention = 311, control = 304). COVID-19 severity ranged: mild n = 155; moderate n= 369; severe n=53; critical n = 38. Intervention dose: clinically stable patients received oral rivaroxaban, 20 mg once daily (15 mg

once daily if reduced creatinine clearance); clinically unstable patients received subcutaneous enoxaparin 1 mg/kg twice per day, or IV unfractionated heparin at a dose to achieve anti-Xa concentration or partial thromboplastin time targets. Unfractionated heparin preferred option for patients with renal dysfunction or disseminated intravascular coagulation. Treatment continued to day 30. Comparison dose: prophylactic doses of enoxaparin or unfractionated heparin. Bias was reported as having some concerns due to lack of blinding and deviations from intended interventions (not all participants received the treatment intended).

Effectiveness of the intervention

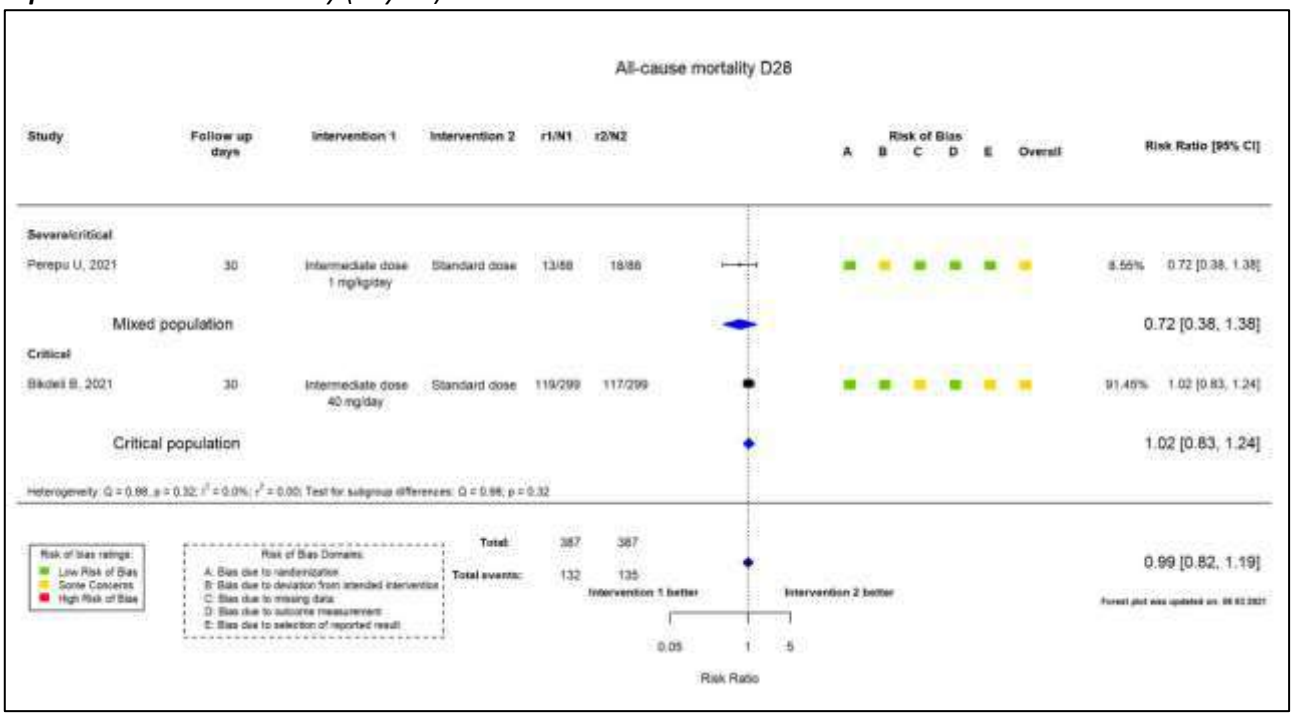
Comparison 1 - intermediate dose anticoagulation compared to standard prophylactic dose anticoagulation

- *Severely/ critically ill population*

Outcomes

1. *All-cause Mortality (day 28):*
   There may be little or no difference in all-cause mortality between those on intermediate compared to standard dose prophylactic anticoagulation RR 0.99 (95% CI 0.82 – 1.19, 2 trials, n = 774, low certainty evidence due to imprecision and some concerns about risk of bias). That is 3 fewer deaths per 1000 people treated with an intermediate dose regimen (ranging from 63 fewer to 66 more deaths).

***Forest plot 1**: All-cause Mortality (day 28):*



2. *Thromboembolic events:*
   2.1 Arterial thrombosis:

Arterial thrombosis	Intermediate dose	Prophylactic dose	Effect size if available	Meta-analysis
Perepu et al	5/88 (6%)	2/88 (2%)	OR 2.56 (95% CI 0.48 – 14.3) (low certainty due to very serious imprecision).	RR 2.50 (95% CI 0.50, 12.54)10 (very low certainty due to very serious imprecision and some concerns about risk of bias)
Inspiration trial	No myocardial infarctions reported and 1 stroke in each group reported.			

2.2 Venous thrombosis:

Venous thrombosis	Intermediate dose	Prophylactic dose	Effect size if available	Meta-analysis
Perepu et al	7/88 (8%)	6/88 (7%)	OR 1.79 (95% CI 0.51 – 6.25)	RR 1.02 (95% CI 0.50, 2.08) (very low certainty due to very serious imprecision and some concerns about risk of bias)
Inspiration trial	9/276 (3.3%)	10/286 (3.5%)	OR 0.93 (95% CI 0.37 – 2.32)	

3. *Bleeding events:*

3.1 Major bleeding:

Major bleeding	Intermediate dose	Prophylactic dose	Effect size if available	Meta-analysis
Inspiration trial	7/276 (2.5%)	4/286 (1.4%)	OR 1.83 (95% CI 0.53 - 5.93) (low certainty due to very serious imprecision).	RR 1.53 (95% CI 0.55 - 4.30) (very low certainty due to very serious imprecision and some concerns with risk of bias)
Perepu et al	2 participants in each group		OR 0.99 (95% CI 0.14 – 7.14) (low certainty due to very serious imprecision).	

4. *Duration of hospitalization*: not reported

5. *Progression to ICU admission*: not reported

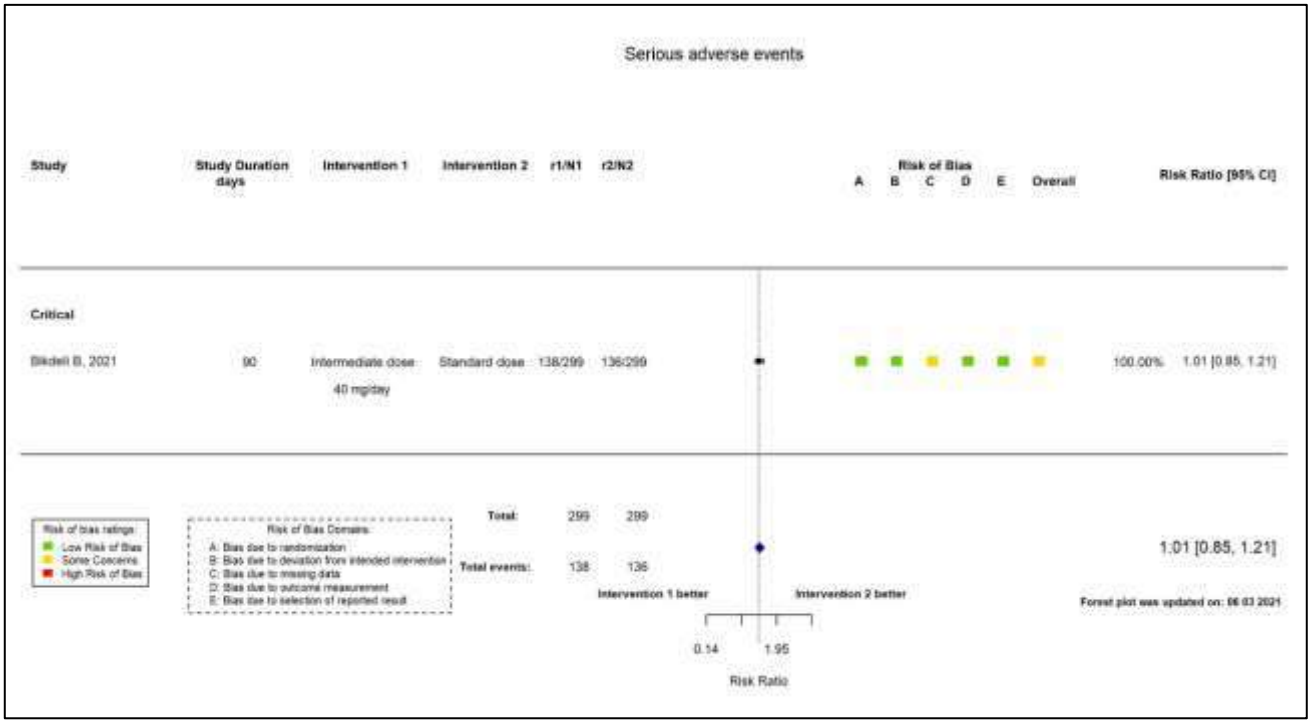
6. *Progression to mechanical ventilation*: not reported

7. *Duration of ICU stay*: not reported

8. *Duration of mechanical ventilation:* not reported

9. *Serious adverse events* (no data for adverse reactions and adverse events):
There may be little or no difference in the number of serious adverse events between intermediate and standard thromboprophylaxis dosing RR 1.01 (95% CI 0.85 – 1.21, 1 trial, n = 598, low certainty evidence). That is 5 more serious adverse events per 1000 people treated with the intermediate dose rather than standard thromboprophylaxis (ranging from 68 fewer to 96 more serious adverse events).

Forest plot 2: *Serious adverse events*



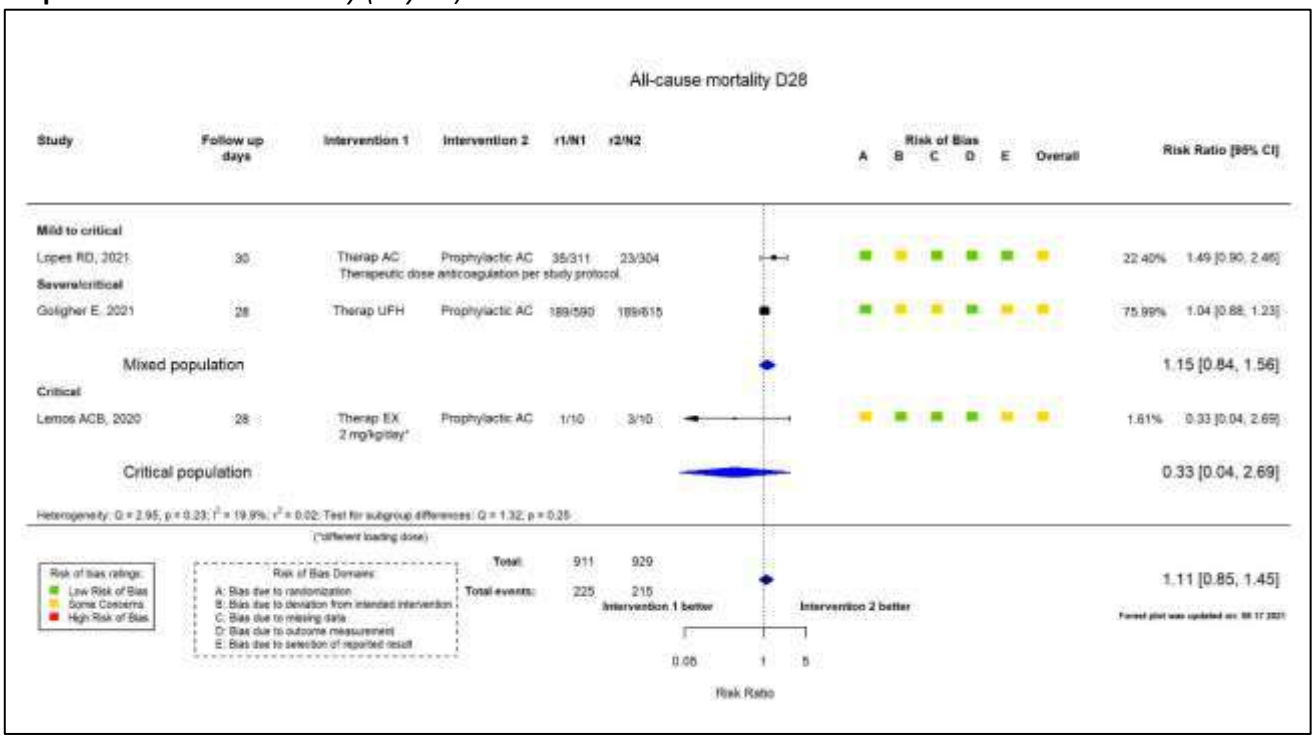
Comparison 2: therapeutic dose anticoagulation compared to standard prophylactic dose anticoagulation

- *Mixed populations (as show in forest plot)*

Outcomes

1. *All-cause Mortality (day 28):*
   The effect of the dosing regimen on death requires further research. He results are based on deaths reported in three trials of mixed population, dominated by severely ill hospitalised population. There may be little or no difference in all-cause mortality between those on intermediate compared to standard dose prophylactic anticoagulation RR 1.11 (95% CI 0.85 – 1.45, 3 trials, n = 1840, low certainty evidence). That is 24 more deaths per 1000 people treated with a therapeutic dose regimen compared to standard prophylaxis regimen (ranging from 35 fewer to 104 more deaths).

Forest plot 3: *All-cause Mortality (day 28):*

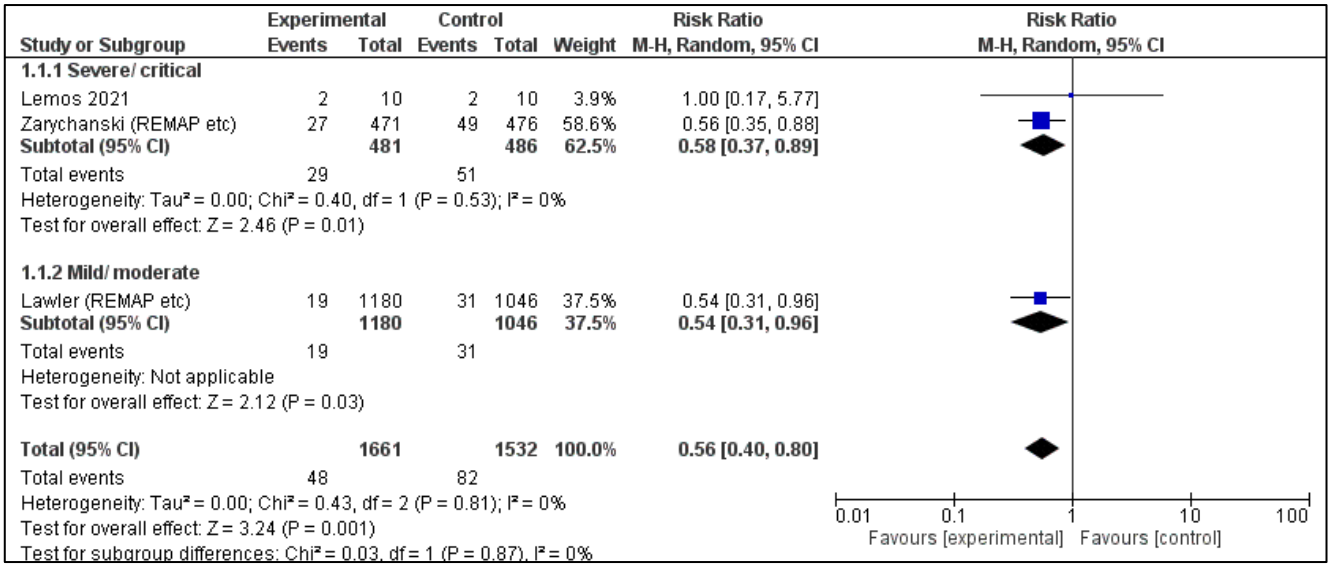


2. *Number of thromboembolic events:*

Major thromboembolic events	Therapeutic anticoagulation	Prophylactic regimen	Effect size
Severe			
Zarychanski	27/471 (5.7%)	49/476 (10.3%)	RR 0.58 (95% CI 0.37 - 0.89)
Lemos	2/10	2/10	
Mild/ moderate			
Lawler	19/1180 (1.6%)	31/1046 (2.9%)	RR 0.54 (95% CI 0.31 - 0.96)
		Overall sub-total	RR 0.56 (95% CI 0.40 -0.80)

*Numbers direct from trial reports, denominators are not based on an ITT, may overestimate effect.

Forest plot 4: *Major thromboembolic events*

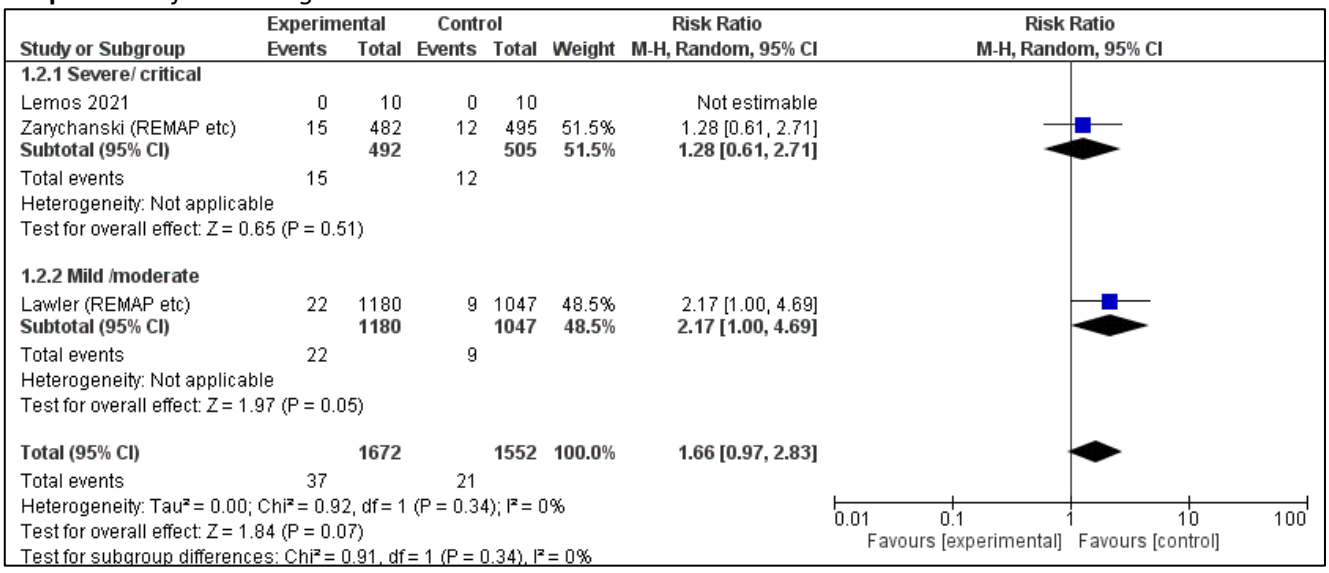


3. *Bleeding events:*

Major bleeding	Therapeutic anticoagulation	Prophylactic regimen	Effect size
Severe			
Zarychanski	15/482 (3.1%)	12/495 (2.4%)	**RR 1.28 (95% CI 0.61 - 2.71)**
Lemos	none reported, minor bleeding: 2/ 10 therapeutic group		N/A
Mild/ moderate			
Lawler	22/1180 (1.8%)	9/1047 (0.01%)	**RR 2.17 (95% CI 1.00 - 4.69)**

*Numbers direct from trial reports, denominators are not based on an ITT, may overestimate effect.

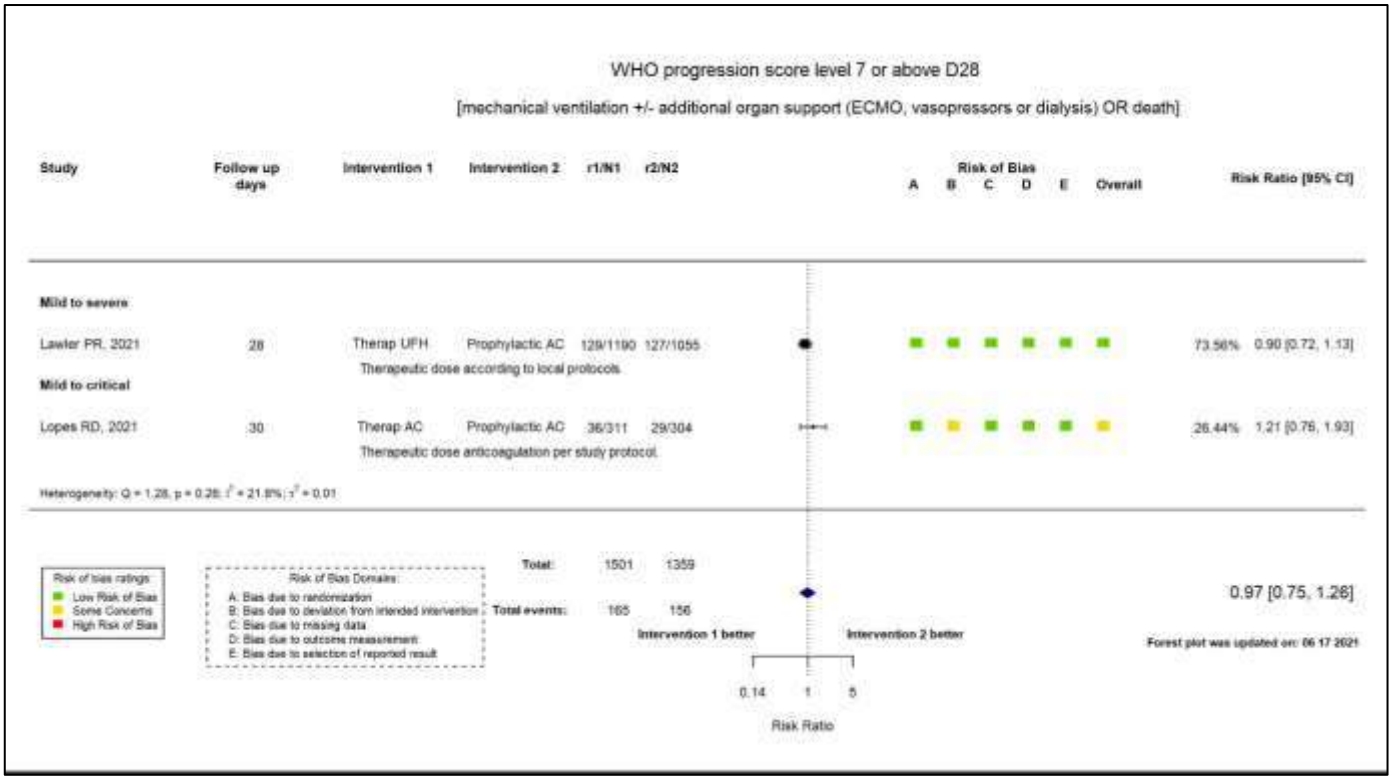
Forest plot 5: *Major bleeding events*



4. *Duration of hospitalization:*
   Lemos et al.: 31 days (IQR 22-35 days) in intervention group vs to 30 days (IQR 23 – 38 days) in prophylaxis group

5. *Progression to ICU admission:*
   WHO progression score (level 7 or above) day 28 [mechanical ventilation; with or without additional organ support (ECMO, vasopressors, or dialysis) or death]: There is probably little or no difference in WHO progression score to level 7 or above between those on intermediate compared to standard dose prophylactic anticoagulation RR 0.97 (95% CI 0.75 – 1.26, 2 trials, n = 2860, moderate certainty evidence). That are 3 fewer people progressing to WHO progression score 7 or above per 1000 people treated with a therapeutic dose regimen compared to standard prophylaxis regimen (ranging from 29 fewer to 30 more events).

Forest plot 6: *WHO progression score (level 7 or above) day 28*



6. *Duration of ICU stay:* not reported

7. *Duration of mechanical ventilation*: not reported

8. *Adverse reactions and adverse events*: not reported

Future clinical trials

As of 16 June 2021, there are 34 registered clinical trials investigating role of optimal dose of heparins for thromboprophylaxis in patients with COVID-19 (www.covid-nma.com). A short summary of planned and ongoing studies is included in Appendix 3.

CONCLUSION

The current evidence about the use of a higher dose (intermediate and therapeutic regimens) for preventing thrombosis in mild/ moderate or severe/ critical hospitalised patients with COVID-19 does not indicate a benefit for higher dosing regimens over the standard thromboprophylaxis treatment dosing. Therefore, the Adult Hospital Level Standard Treatment Guidelines and Essential Medicines List recommendation stands for thromboprophylaxis dosing in patients with moderate to high risk of developing venous thromboembolism[20] (See Appendix 1).

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Declaration of interests:

RW and KC have no interests to declare. SM is employed by the Ophthalmological Society of South Africa, which receives sponsorships, grants and support for CPD activities, conferences, meetings and registry activities from various companies.

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Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias
Comparison 1: Intermediate dose vs standard thromboprophylaxis dose					
INSPIRATION Investigators. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA. 2021;325(16):1620-30.	Multicentre Randomised Controlled Trial with a 2x2 factorial design Single blinded Recruitment 29 July 2020 to 19 November 2020 Follow up 30 days for primary outcome.	10 academic centres in Iran Patients: Adult patients (≥18 years) PCR-confirmed COVID-19 and admitted to ICU within 7 days of initial hospitalization. Sample size: 562 participants (325 males, 273 females); median (IQR) age: 62 (50-71) years. **Intermediate dose arm**: n = 276; median (IQR) age = 62 (51-70.7) years **Standard dose arm**: n = 286; median (IQR) age = 61 (47-71) years.	**Intermediate dose arm:** Intermediate-Dose prophylactic anticoagulation Enoxaparin: 1 mg/kg once daily for 30 days (if weight < 120kg and creatinine clearance > 30 ml/min). **Standard dose arm:** Standard-Dose prophylactic anticoagulation. Notes: The primary anticoagulant agent in both groups was enoxaparin. Unfractionated heparin was used in the case of severe kidney insufficiency. For patients who weighed less than 120 kg and had a creatinine clearance greater than 30 mL/min, enoxaparin, 1 mg/kg daily, was assigned as intermediate-dose anticoagulation. Enoxaparin, 40 mg daily, was the control group standard-dose prophylactic anticoagulation regimen. In both groups, predefined modifications were advised according to body weight and creatinine clearance. The assigned treatments were planned to be continued until the 30-day follow-up, irrespective of hospital discharge status.	Primary outcomes: -acute VTE, arterial thrombosis, -treatment with extracorporeal membrane oxygenation (ECMO) -all-cause mortality within 30 days of enrollment. Secondary outcomes: -all-cause mortality, -adjudicated VTE, and ventilator-free days. Prespecified exploratory outcomes included: -objectively clinically diagnosed type I acute myocardial infarction -stroke, -acute peripheral arterial thrombosis -rate of discharge from the ICU; -incident atrial fibrillation; -new in-hospital kidney replacement therapy; and -ICU length of stay. The primary outcomes occurred in 126 patients (45.7%) in the intermediate-dose group and 126 patients (44.1%) in the standard-dose prophylaxis group (absolute risk difference, 1.5% [95% CI, −6.6% to 9.8%]; odds ratio, 1.06 [95% CI, 0.76-1.48]; *P* = .70). Major bleeding occurred in 7 patients (2.5%) in the intermediate-dose group and 4 patients (1.4%) in the standard-dose prophylaxis group (risk difference, 1.1% [1-sided 97.5% CI, −∞ to 3.4%]; odds ratio, 1.83 [1-sided 97.5% CI, 0.00-5.93]), not meeting the	Overall Risk of Bias: Some concerns for the following items: Missing outcome data: some concerns Selection of the reported results – some concerns Deviations from intervention: Some concerns Comments: In addition to the published articles, the trial registry, published and full protocol and statistical analysis plan were used in data extraction and assessment of risk of bias. There were no substantive differences between the published article and the trial registry and protocol in population, procedures and interventions. One long term outcome, included in the trial registry but not the protocol (post-COVID-19 functional status at 60 & 90 days), is not reported. All other outcomes for the reported comparison in the trial registry and protocol were reported. Some post hoc subgroup analyses were performed. Recruitment was paused by the data and safety monitoring board because of futility for efficacy and potential excess of safety events. On 30th of April, 2021, this study (90 Day results) was updated based on the published report in Thromb Haemost.

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias
				noninferiority criteria (*P* for noninferiority >.99). Severe thrombocytopenia occurred only in patients assigned to the intermediate-dose group (6 vs 0 patients; risk difference, 2.2% [95% CI, 0.4%-3.8%]; *P* = .01).	
Perepu U et al Standard Prophylactic Versus Intermediate Dose Enoxaparin in Adults with Severe COVID-19: A Multi-Center, Open-Label, Randomised Controlled Trial. Available at SSRN: https://ssrn.com/abstract=3840099 or http://dx.doi.org/10.2139/ssrn.3840099	RCT Unblinded Follow-up duration (days): 30	N= 17699 males and 77 females median age 64 years (range 24 to 86); 14% were Hispanic, 6% were African American, and 76% were Whites Standard dose, N=86, Mean (range), 63.5 (30-85) Intermediate dose N=87 Mean (range), 65 (24-86) Eligibility: Adults 18 years of age or older; SARS-CoV-2 infection confirmed by nasopharyngeal swab polymerase chain reaction; requiring hospitalization; admitted to an ICU and/or had a modified ISTH Overt DIC score ≥ 3 Exclusion criteria Indication for full therapeutic dose anticoagulation or they had active major bleeding; severe thrombocytopenia (platelet count <25,000/uL); current pregnancy; a history of acute venous or arterial thrombosis within the prior 3 months; or acute or chronic renal insufficiency with an estimated creatinine clearance less than 30 mL/min calculated by the modified Cockcroft and Gault formula	Intermediate-Dose Enoxaparin 1 mg/kg daily if BMI < 30; 0.5 mg/kg twice daily if BMI ≥ 30; subcutaneously. (n = 88) **Compared to** Standard-Dose prophylactic was 40 mg subcutaneous daily in BMI was less than 30 and 30mg SC twice daily for non-ICU patients or 40 mg twice daily for ICU patients with BMI more than 30 anticoagulation (n = 88)	**Primary outcome** All-cause mortality at 30 days. Time-to death with censoring at 30 days 18(21%) in standard dose 13(15%) in intermediate dose Odds ratio (95%CI) 0.66 (0.30-1.65), p=0.302 **Secondary outcome** Acute kidney injury, defined as estimated creatinine clearance less than 30 ml/min, arterial or venous thrombosis confirmed with imaging, major bleeding, and minor bleeding. Acute kidney injury occurred in 15 patients in the standard dose group and in 11 patients in the intermediate dose group Odds ratio (95%CI) 0.68 (0.29-1.59), p=0.377	Overall Risk of Bias: **Some concerns** for the following items: Due to some analysis issues and the ITT, however, not major issues In addition to the pre-print article, the trial registry was used in data extraction and assessment of risk of bias. Neither protocol nor statistical analysis plan was available at time of extraction. There were some differences between inclusion criteria in the registry and the article: the registry required a modified ISTH Overt DIC score ≥ 3 whereas in the article the criteria included admitted to an ICU and/or a modified ISTH Overt DIC score ≥ 3. Several secondary outcomes in the registry were not reported (Packed Red Blood Cell Transfusions, Platelet Transfusions, Fresh Frozen Plasma Transfusions, Cryoprecipitate Transfusions, Prothrombin Complex Concentrate Transfusions) while other reported secondary outcomes (acute kidney injury, ischemic stroke and myocardial infarction) were not in the registry. Exploratory laboratory biomarker outcomes will be reported separately. The study achieved its target sample size.
Therapeutic dosing compared to standard thromboprophylaxis dosing					

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias
Zarychanski R. Therapeutic Anticoagulation in Critically Ill Patients with Covid-19 – Preliminary Report. medRxiv. 2021:2021.03.10.21252749. Pre-print	an open-label, adaptive, multiplatform, randomized, clinical trial of three participating platforms 1) Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community Acquired Pneumonia (REMAP-CAP; NCT02735707) 2) Accelerating Covid-19 Therapeutic Interventions and Vaccines-4 Antithrombotics Inpatient platform trial (ACTIV-4a; NCT04505774 and NCT04359277) 3)Antithrombotic Therapy to Ameliorate Complications of Covid-19 (ATTACC; NCT04372589)	Patients hospitalized for covid-19. Severe covid-19 patients who were given intensive care unit-level respiratory or cardiovascular organ support (high flow nasal oxygen ≥ 20 L/min, non-invasive or invasive mechanical ventilation, extracorporeal life support, vasopressors, or inotropes). Sample size: n = 1205 males: 762, females: 327 Therapeutic anticoagulation N=532 Mean (SD) age 60.2 (13.1) Usual care pharmacological thromboprophylaxis N=557 Mean (SD) age 61.6 (12.5) Exclusion criteria- Patients admitted to the ICU with Covid-19 for more than 48 hours (REMAP-CAP) or to hospital for more than 72 hours (ACTIV-4a, ATTACC) prior to randomization, at imminent risk of death without an ongoing commitment to full organ support, at high risk of bleeding, receiving dual antiplatelet therapy, had a separate clinical indication for therapeutic anticoagulation, or had a history of heparin sensitivity including heparin-induced thrombocytopenia.	**Therapeutic Anticoagulation Arm** It was administered according to local site protocols for the treatment of acute venous thromboembolism for up to 14 days or recovery (defined as hospital discharge, or liberation from supplemental oxygen for at least 24 hours). **Usual care** **pharmacological thromboprophylaxis** was administered according to local practice or with guidance from the trial protocol on maximum dosing, which included either standard low dose thromboprophylaxis or enhanced intermediate dose thromboprophylaxis**.**	**Primary outcome** organ support-free days (OSFDs) made up of 1) survival to hospital discharge and 2) in survivors, the number of days free of organ support to day 21 A higher value of OSFD was considered a better outcome. Patients discharged from hospital prior to day 21 was assumed to be alive and free of organ support through 21 days **Secondary outcome** Survival to day 90 major thrombotic events or death (a composite of myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death) through to day 28 (ACTIV-4a, ATTACC) or through to hospital discharge (REMAP-CAP). **Safety outcomes** 1) Major bleeding during the treatment period as defined by the International Society of Thrombosis and 2) Haemostasias for non-surgical patients17 and laboratory confirmed heparin-induced thrombocytopenia. In the therapeutic group, the median value for organ support free days was 3 (interquartile range -1, 16) In the control group, median value was 5 (interquartile range –1, 16). The median adjusted proportional odds ratio for the effect of therapeutic anticoagulation on organ support-free days was 0.87 (95% CI 0.70-1.08) Secondary outcomes: In-hospital survival was 64.3% in participants	Overall Risk of Bias: **Some concerns** In addition to the pre-print article, the study registries, protocol, and statistical analysis plan were used in data extraction and risk of bias assessment. The article reports preliminary results for the severe/critical subgroup of patients in three international adaptive platform trials with harmonized protocols that evaluated the effect of an anticoagulation protocol using predominantly therapeutic dosing versus standard anticoagulation using predominantly prophylactic dosing. The three trials were REMAP-CAP (NCT02735707), ACTIV-4a (NCT04505774 and NCT04359277), and ATTACC (NCT04372589). The individual trial registries reflect each trial's individual primary objectives, while the harmonized protocol reflects the objectives of this comparison. There were no major differences in population, procedures and intervention between the protocol and the pre-print article, and the outcomes reported are appropriate for a preliminary report. The additional analyses specified in the statistical analysis plan will be presented with the final report when more detailed long term outcome data are available. Recruitment of severe/critical patients was halted after interim analysis revealed futility.

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias
				assigned to therapeutic anticoagulation and 65.3% in participants assigned to usual care pharmacological thromboprophylaxis (median adjusted odds ratio 0.88, 95% CI 0.67-1.16).	
Lemos A, Douglas Alexandre Salvetti, Maísa Cabetti Gilio, Renato Noffs Agra, Lucas Barbosa Pazin-Filho, Antonio Miranda, Carlos Henrique,. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thrombosis Research. 2020;196:359-66.	randomized, open-label single-center, phase II trial April 2020 to July 2020	Adult patients 18 years and older with PCR confirmed COVID-19 with acute respiratory distress syndrome (ARSD), Sample size=20 (17 males and 3 females) **Therapeutic arm**, n=10, Mean (SD) age 55 (10) years **Prophylactic arm**, n=10, Mean (SD) age 58 (16) years **Inclusion criteria** respiratory failure requiring mechanical ventilation. D-dimer levels greater than 1000 µg/L; prothrombin time/international normalized ratio (INR) < 1.5; activated partial thromboplastin time (aPTT)/ratio < 1.5, and platelet count greater than 100,000/mm3. **exclusion criteria** Older than 85 years creatinine clearance (CrCl) < 10 mL/min, severe circulatory shock with a dose of norepinephrine higher than 1.0 µg/kg/min, chronic renal failure in renal replacement therapy, Child B and C chronic liver disease, advanced diseases, such as active cancer, heart failure with functional class III and IV. pregnant women, recent major surgery or severe trauma in the last 3 weeks, recent stroke in the last 3 months, active bleeding, blood dyscrasia such as hemophilia	**Therapeutic group** Subcutaneous Enoxaparin with dose being adjusted according to age and creatinine clearance Patients under 75 years-old with CrCl > 50 mL/min received 1 mg/Kg BID; Patients with CrCl between 30 and 50 mL/min: 0.75 mg/Kg BID; Patients with CrCl between 10 and 30 mL/min: 1 mg/Kg OD Patients older than 75 years with CrCl > 50 mL/min received: 0.75 mg/Kg BID; with CrCl between 30 and 50 mL/min: 1 mg/Kg OD; with CrCl between 10 and 30 mL/min: 0.75 mg/Kg OD; **standard thromboprophylaxis group** received SC unfractionated heparin (UFH) at a dose of 5000 IU TID (if weight < 120 kg) and 7500 IU TID (if weight > 120 kg) or enoxaparin at a dose of 40 mg OD (if weight < 120 kg) and 40 mg BID (if weight > 120 Kg) according to the doctor's judgment.	**Primary outcome** variation in gas exchange over time evaluated through the ratio of partial pressure of arterial oxygen(PaO2) to the fraction of inspired oxygen (FiO2) at baseline, 7, and 14 days after randomization. statistically significant increase over time in the PaO2/FiO2 ratio among the patients in the therapeutic enoxaparin group was observed (163 [95% CI 133–193] at baseline; 209 [95% CI 171–247] after 7 days; and 261 [95% CI 230–293] after 14 days), p = 0.0004. But no statistically significant difference was observed in the standard thromboprophylaxis group **Secondary outcome** the time until successful liberation from mechanical ventilation, the ventilator-free days (during the 28 days after inclusion in the study; numbers of days without mechanical ventilation), the variation in D-dimer levels collected at baseline during inclusion in the study and repeated 72–96 h later, all cause 28-day mortality, in-hospital mortality, and the intensive care unit (ICU)-free days at 28 days.	Overall Risk of Bias: **Some concerns** for the following items: retrospective registration of the study and no available statistical analysis plan. Some concerns for the outcome mortality. The third arm of the study mentioned in the protocol was abandoned The evaluation of the outcome stated in the protocol as Evaluation of gas exchange between D0 / D4 evaluated was changed to the ratio of partial pressure of arterial oxygen (PaO2) to the fraction of inspired oxygen (FiO2) at baseline, 7, and 14 days after randomization. The secondary outcome in the protocol as Evaluation of plasma D-dimer levels between days D0 / D4; Evaluation of circulating levels of the biomarkers of endothelial glycocalyx lesion was changed to the time until successful liberation from mechanical ventilation, the ventilator-free days and D-dimer levels collected at baseline during inclusion in the study and repeated 72–96 h later, allcause 28-day mortality, in-hospital mortality, and the intensive care unit (ICU)-free days at 28 days.

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias
Lawler PG, et al,. Therapeutic Anticoagulation in Non-Critically Ill Patients with Covid-19. medRxiv. 2021:2021.05.13.21256846. (preprint) Trial registration numbers NCT02735707, NCT04505774, NCT04359277, NCT04372589	RCT Unblinded Multicentre trial: Australia, Brazil, Canada, Mexico, Nepal, Netherlands, Spain, UK, USA Follow up 90 days Enrolment from April 2020 and early termination on January 2021 for futility.	2245 participants (n_1=1190 / n_2= 1055) including **non-critically ill** hospitalized patients, **Characteristics of participants** N=2245 Mean age : 58.9 1310 males Severity : Mild: n=* / Moderate: n=*/ Severe: n=98 Critical: n=0 Inclusion criteria: Adults hospitalized for Covid-19 (≥18 years in ACTIV-4a and ATTACC, not specified in REMAP-CAP); Suspected or confirmed SARS-CoV-2 infection with intent to test for COVID-19 in REMAP-CAP, confirmed SARS-CoV-2 infection in ACTIV-4a and ATTACC; expected hospital LOS > 48 hours in REMAP-CAP, expected hospital LOS ≥ 72 hours in ACTIV-4a and ATTACC; <48 hours from admission in REMAP-CAP, <72 hours in ACTIV-4a and ATTACC. If the patient is already hospitalized and the COVID-19 diagnosis is due to an outbreak or an incidental finding, then enrollment can occur within 72 hours of a clinical syndrome attributable to COVID-19 that requires continued hospitalization (e.g. new or worsening oxygen requirements or acute kidney injury) which is further anticipated to extend the hospital admission by an additional 72 hours from randomization Exclusion Discharge expected within 48 hours (REMAP-CAP) or 72 hours (ACTIV-4a and ATTACC); clinical indication for therapeutic anticoagulation ; high risk for bleeding ; required dual antiplatelet therapy ; history of heparin allergy including heparin-induced thrombocytopenia.	**Intervention:** Therapeutic Heparin Therapeutic dose low molecular weight or unfractionated heparin administered according to local protocols used for the treatment of acute venous thromboembolism for up to 14 days or until recovery. **Comparison** Prophylactic anticoagulant	The trial was stopped when prespecified criteria for superiority were met for therapeutic-dose anticoagulation in groups defined by high (≥2-fold elevated) and low (<2-fold elevated) Ddimer. Among 2219 participants in the final analysis, the probability that therapeutic anticoagulation increased organ support-free days compared to thromboprophylaxis was 99.0% (adjusted odds ratio 1.29, 95% credible interval 1.04 to 1.61). The adjusted absolute increase in survival to hospital discharge without organ support with therapeutic-dose anticoagulation was 4.6% (95% credible interval 0.7 to 8.1). In the primary adaptive stopping groups, the final probabilities of superiority for therapeutic anticoagulation were 97.3% in the high D-dimer group and 92.9% in the low D-dimer group. Major bleeding occurred in 1.9% and 0.9% of participants randomized to therapeutic anticoagulation and thromboprophylaxis, respectively.	Overall Risk of Bias: **Some concerns** related to lack of blinding and mainly affecting the more subjectively ascertained outcome 'clinical improvement', not one of the critical outcome for our decisions. Overall low risk of bias for mortality and WHO score 7 and above. The available evidence is in a pre-print and we await peer review.
Lopes RD, de Barros e Silva PGM, Furtado RHM, Macedo AVS, Bronhara B,	Multicentre open label RCT in Brazil	N = 615 Intervention = 311 Comparison = 304 Mean age: 56.6	**Intervention**	The primary efficacy outcome was a hierarchical analysis of time to death, duration of hospitalisation, or	Overall Risk of Bias: **Some concerns** This relates to lack of blinding and deviations from intended interventions. Both arms received

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias
Damiani LP, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. The Lancet. 2021;397(10291):2253-63. NCT04394377	Recruitment: June 24, 2020, to Feb 26, 2021 Funding: Mixed (Coalition COVID-19 Brazil, Bayer SA.)	368 males Severity: Mild: n = 155 / Moderate: n= 369 / Severe: n=53 Critical: n = 38 Inclusion: Hospitalised; ≥ 18 years old ; confirmation of COVID-19; symptoms for up to 14 days; elevated D-dimer concentration (above the upper limit of normal reference range per local laboratory).	Clinically stable patients: PO rivaroxaban, 20 mg once daily (15 mg once daily if reduced creatinine clearance). Clinically unstable patients: SC enoxaparin 1 mg/kg twice per day, or IV unfractionated heparin at a dose to achieve anti-Xa concentration or partial thromboplastin time targets. Unfractionated heparin preferred option for patients with renal dysfunction or disseminated intravascular coagulation. Treatment to day 30. **Comparison:** Prophylactic anticoagulation with enoxaparin or unfractionated heparin	duration of supplemental oxygen to day 30. No difference in primary efficacy outcome between therapeutic or prophylactic anticoagulation, with 28 899 (34·8%) wins in the therapeutic group and 34 288 (41·3%) in the prophylactic group (win ratio 0·86 [95% CI 0·59–1·22], p=0·40). Consistent results were seen in clinically stable and clinically unstable patients. The primary safety outcome of major or clinically relevant non-major bleeding occurred in 26 (8%) patients assigned therapeutic anticoagulation and seven (2%) assigned prophylactic anticoagulation (relative risk 3·64 [95% CI 1·61–8·27], p=0·0010). Allergic reaction to the study medication occurred in two (1%) patients in the therapeutic anticoagulation group and three (1%) in the prophylactic anticoagulation group.	anticoagulation, but the majority of the intervention group (94.8%) received therapeutic dose anticoagulation while the majority of the control group received prophylactic dose anticoagulation during hospitalization (99.5%), while 13% were prescribed extended prophylaxis beyond hospital discharge

Table 2. Evidence profile table for comparison: intermediate vs prophylactic dosing for COVID-19 patients requiring organ support

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulants at intermediate-intensity	prophylactic-intensity	Relative (95% CI)	Absolute (95% CI)		
Death												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	132/387 (34.1%)	135/387 (34.9%)	**RR 0.99** (0.82 to 1.19)	**3 fewer per 1,000** (from 63 fewer to 66 more)	⨁⨁◯◯ LOW	CRITICAL
Arterial thrombosis												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	5/88 (5.7%)	2/88 (2.3%)	**RR 2.50** (0.50 to 12.54)	**34 more per 1,000** (from 11 fewer to 262 more)	⨁◯◯◯ VERY LOW	CRITICAL
Venous thrombosis												
2	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	16/364 (4.4%)	16/374 (4.3%)	**RR 1.02** (0.50 to 2.08)	**1 more per 1,000** (from 21 fewer to 46 more)	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding												
2	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	9/364 (2.5%)	6/374 (1.6%)	**RR 1.53** (0.55 to 4.30)	**9 more per 1,000** (from 7 fewer to 53 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	138/299 (46.2%)	136/299 (45.5%)	**RR 1.01** (0.85 to 1.21)	**5 more per 1,000** (from 68 fewer to 96 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. Risk of bias downgraded by 1 level: some concern regarding deviation from intended intervention, missing data and selection of reported results.

b. Imprecision downgraded by 1 level: due to small sample size.

c. Very small number of events and patients included in the intervention studies, lowering the certainty by two levels for imprecision

Table 3. Evidence profile table for comparison: therapeutic vs prophylactic intensity dosing for hospitalized patients with COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulants at therapeutic-intensity	prophylactic-intensity	Relative (95% CI)	Absolute (95% CI)		
Death												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	225/911 (24.7%)	215/929 (23.1%)	**RR 1.11** (0.85 to 1.45)	**25 more per 1,000** (from 35 fewer to 104 more)	⊕⊕◯◯ LOW	CRITICAL
Major thromboembolic events												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48/1661 (2.9%)	82/1532 (5.4%)	**RR 0.56** (0.40 to 0.80)	**24 fewer per 1,000** (from 32 fewer to 11 fewer)	⊕⊕◯◯ LOW	CRITICAL
Major bleeding												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	37/1672 (2.2%)	21/1552 (1.4%)	**RR 1.66** (0.97 to 2.83)	**9 more per 1,000** (from 0 fewer to 25 more)	⊕⊕◯◯ LOW	CRITICAL
WHO Progression score 7 or above (follow up: 28 days)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	165/1501 (11.0%)	156/1359 (11.5%)	**RR 0.97** (0.75 to 1.26)	**3 fewer per 1,000** (from 29 fewer to 30 more)	⊕⊕◯◯ LOW	

CI: *Confidence interval;* ***RR:*** *Risk ratio;* ***OR:*** *Odds ratio*

Explanations

a. Risk of bias downgraded by 1 level: some concern regarding deviation from intended intervention, missing data and selection of reported results.

b. Imprecision downgraded by 1 level: due to small sample size.

Appendix 1: GUIDELINE CONSIDERATIONS

World Health Organization: Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected. Interim guidance (25 January 2021)[13]:

Prevention of complications in hospitalized and critically ill patients with COVID-19

In hospitalized patients with COVID-19, without an established indication for higher dose anticoagulation, we suggest administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing (conditional recommendation, very low certainty).

Quick link to evidence to decision table: https://covid19.recmap.org/recommendation/0bf8945e-1229-4155-8970-d90cf8f6cde2

NIH COVID-19 Treatment Guidelines (updated 11 February 2021)[12]

Venous Thromboembolism Prophylaxis

For non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (AIII).

Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation (AIII) (see the recommendations for pregnant individuals below). Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 (AIII).

There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.

Hospitalized patients with COVID-19 should not routinely be discharged from the hospital while on VTE prophylaxis (AIII). Continuing anticoagulation with a Food and Drug Administration-approved regimen for extended VTE prophylaxis after hospital discharge can be considered for patients who are at low risk for bleeding and high risk for VTE, as per the protocols for patients without COVID-19 (see details on defining at-risk patients below) (BI).

There are currently insufficient data to recommend either for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers.

For hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion, the possibility of thromboembolic disease should be evaluated (AIII). **(Level of Evidence: Expert Opinion)**

American Society of Hematology: (updated 20 July 2020)[14]

Recommendation for VTE prophylaxis in patients with COVID-19

All hospitalized adults with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH over unfractionated heparin to reduce contact, unless the risk of bleeding outweighs the risk of thrombosis. In the setting of heparin-induced thrombocytopenia, fondaparinux is recommended. Dose adjustment for obesity may be used per institutional guidance. In patients where anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (e.g. pneumatic compression devices). Combined pharmacologic and mechanical prophylaxis is not generally recommended.

Despite the lack of quality published evidence, many institutional protocols have adopted an intermediate-intensity (i.e., administering the usual daily LMWH dose twice daily) or even a therapeutic-intensity dose strategy for thromboprophylaxis based on local experience. We recommend participation in well-designed clinical trials and/or epidemiologic studies when they become available.

Recommendation regarding empiric therapeutic-intensity anticoagulation for VTE prophylaxis in seriously ill COVID-19 patients (i.e. in the absence of confirmed or suspected VTE)

Microvascular thrombosis is hypothesized to be involved in hypoxemic respiratory failure in some patients with COVID-19. Autopsy studies to date have been limited but they do show large vessel and microvascular thrombosis, pulmonary hemorrhage and high prevalence of VTE. Although retrospective cohort studies of patients treated or not treated with anticoagulation have been published, such observational data should not be used to support changes in practice due to the survivor bias, confounding by indication, and lack of adjustment for important patient comorbidities and other treatments. Whether critically ill COVID-19 patients should receive therapeutic-intensity anticoagulation in the absence of confirmed or suspected VTE is currently unknown. Multiple randomized controlled trials are investigating the effects of different doses of heparin on patient outcomes. We encourage participation in clinical trials rather than

empiric use of therapeutic-dose heparin in COVID-19 patients with no other indication for therapeutic dose anticoagulation.

Australian guidelines for the clinical care of people with COVID-19. Version 17.0 [15]

10 Anticoagulants

10.1 Venous thromboembolism (VTE) prophylaxis

Consensus recommendation

Use prophylactic doses of anticoagulants, preferably low molecular weight heparin (LMWH) (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) in adults with **moderate, severe or critical COVID-19** or other indications, unless there is a contraindication, such as risk for major bleeding. Where the estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73m2, unfractionated heparin or clearance-adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily or dalteparin 2500 IU once daily).

Increased-dose venous thromboembolism (VTE) prophylaxis

Do not routinely offer therapeutic anticoagulant dosing in adults with severe or critical COVID-19. There is no additional indication for therapeutic dosing for anticoagulants in adults with severe or critical COVID-19 beyond current standard best practice. (**conditional recommendation against**)

The Task Force is currently reviewing emerging trial data on this.

Hospital level (Adults) Standard Treatment Guidelines and Essential Medicines List[24]

2.8 VENOUS THROMBO-EMBOLISM

MEDICINE TREATMENT

PROPHYLAXIS

Risk Assessment

Risk assessment is essential, and treatment needs to be individualised. Risk factors for VTE can be divided into predisposing factors (i.e. patient characteristics) and exposing factors (i.e. underlying medical conditions, nature of surgical intervention, etc.).

SUBCATEGORIES OF VTE RISK IN SURGICAL AND NON-SURGICAL PATIENTS

	Surgical patients	***Medical patients***
Low VTE risk	» Surgery lasting <30 minutes » Injuries without or with only minor soft-tissue trauma » No or only minor additional predisposing risk factors	» Infection or acute inflammatory diseases without bed rest » Central venous catheters » No or only minor additional predisposing risk factors
Moderate VTE risk	» Surgical procedures of longer duration » Immobilisation of lower limb with plaster cast » Lower limb arthroscopic procedures. » No or only minor additional predisposing risk factors	» Acute cardiac insufficiency (NYHA III/IV) » Acute decompensated COPD without ventilation » Infection or acute inflammatory diseases with bed rest » Malignant disease » No or only minor additional predisposing risk factors
High VTE risk	» Major surgical procedures for malignancy » Multiple trauma or severe trauma of the spine, vertebra or » lower limbs » Major orthopaedic surgery, e.g. hip or knee replacement » Major surgical procedure of cardiothoracic and pelvic region	» Stroke with paralysis » Acute decompensated COPD with ventilation » Sepsis » ICU patients

Source: Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7. https://www.ncbi.nlm.nih.gov/pubmed/23547704

Some risk assessment models for assessing VTE risk:

Model	Url link to tool
Padua Prediction Score	https://www.mdcalc.com/padua-prediction-score-risk-vte
IMPROVE VTE risk score	https://www.outcomes-umassmed.org/IMPROVE/risk_score/vte/index.html
Geneva risk score	https://www.mdcalc.com/geneva-risk-score-venous-thromboembolism-vte-prophylaxis

Prophylactic treatment

Prophylaxis is indicated for medical patients with moderate to high risk of VTE (see table above), with restricted mobility during acute illness/ surgical patients.

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.

In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist
In renal failure (eGFR <30 mL/minute), the recommended dose of LMWH is 1 mg/kg daily.

OR

Unfractionated heparin, SC, 5 000 units 12 hourly.

Although the risk of bleeding is small, in the following patients prophylaxis should only be used under exceptional circumstances:

» active bleeding
» intraocular, intracranial or spinal surgery
» lumbar puncture or spinal/epidural anaesthesia within 12 hours after prophylactic dose or 24 hours of full therapeutic dose, [Timing of anticoagulants for patients receiving anaesthesia: See section 12.8: Spinal (intrathecal) anaesthesia]
» renal insufficiency
» coagulopathy
» uncontrolled hypertension

Accessible at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Appendix 2: Search strategy

A: Original Review (June 2020)

Total: 88 records excluding duplicates

Epistemonikos

(title:(heparin* OR "heparinic acid" OR liquaemin OR UFH OR "low-molecular-weight heparin" OR LMWH OR dalteparin OR enoxaparin OR nadroparin OR tinzaparin) OR abstract:(heparin* OR "heparinic acid" OR liquaemin OR UFH OR "low-molecular-weight heparin" OR LMWH OR dalteparin OR enoxaparin OR nadroparin OR tinzaparin)) AND (title:(coronivir* OR coronavirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR "COVID-19" OR COVID19 OR "2019-nCOV" OR 2019nCov OR "cv-19" OR"n-COV" OR ncov* OR hCOV* OR "SARS cov-2" OR "SARS-coronavirus" OR "SARS-cov" OR "MERS-cov" OR "MERS cov" OR "severe acute respiratory syndrome coronavirus") OR abstract:(coronivir* OR coronavirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR "COVID-19" OR COVID19 OR "2019-nCOV" OR 2019nCov OR "cv-19" OR"n-COV" OR ncov* OR hCOV* OR "SARS cov-2" OR "SARS-coronavirus" OR "SARS-cov" OR "MERS-cov" OR "MERS cov" OR "severe acute respiratory syndrome coronavirus"))

Records retrieved: 23 records

PubMed

((heparin[mh] OR heparin*[tiab] OR heparinic acid[tiab] OR liquaemin[tiab] OR UFH[tiab] OR heparin, low-molecular-weight[mh] OR LMWH[tiab] OR dalteparin[tiab] OR enoxaparin[tiab] OR nadroparin[tiab] OR tinzaparin[tiab]) AND (coronavir*[tiab] OR coronovirus*[tiab] OR corona virus[tiab] OR virus corona[tiab] OR corono virus[tiab] OR virus corono[tiab] OR COVID-19[tiab] OR COVID19[tiab] OR 2019-nCov[tiab] OR 2019nCov[tiab] OR cv-19[tiab] OR n-cov[tiab] OR ncov*[tiab] OR hCOV*[tiab] OR SARS cov-2[tiab] OR SARS-coronavirus[tiab] OR SARS-cov[tiab] OR (wuhan*[tiab] AND (virus[tiab] OR viruses[tiab] OR viral[tiab])) OR (COVID*[tiab] AND (virus[tiab] OR viruses[tiab] OR viral[tiab])) OR MERS-cov[tiab] OR MERS cov[tiab] OR COVID-19[NM] OR severe acute respiratory syndrome coronavirus 2[nm])) NOT ((animals[mh] NOT humans[mh])) AND (2019/12/01:2020/05/27[dp])

Records retrieved: 55 records

L-OVE Working Group (https://app.iloveevidence.com/)

Type of question: Treatment or prevention
Population: Coronavirus infection
Treatment: Heparins

Records retrieved: 4 records

Cochrane COVID Study Register (https://covid-19.cochrane.org/)

heparin* OR "heparinic acid" OR liquaemin OR UFH OR "low-molecular-weight heparin" OR LMWH OR dalteparin OR enoxaparin OR nadroparin OR tinzaparin

Records retrieved: 46 records

B: Updated review (August 2020)

Total: 189 records excluding duplicates

Cochrane COVID Study Register (https://covid-19.cochrane.org/)
heparin* OR "heparinic acid"

Records retrieved: 111 records, 45 duplicates

Epistemonikos (https://app.iloveevidence.com/**)**
antithrombotic agents

Records retrieved: 116 records, 1 duplicate

C: Updated review search strategy (April 2021)

Epistemonikos (https://app.iloveevidence.com/**)**
22 April 2021

Type of question: **Treatment or prevention**

Intervention: **Heparins**

Records retrieved: 18 systematic reviews, 75 randomised trials

Cochrane COVID Study Register (https://covid-19.cochrane.org/)

Date searched: 1 August 2020 – 22 April 2021

Search strategy:heparin* OR "heparinic acid" OR liquaemin OR UFH OR "low-molecular-weight heparin" OR LMWH OR dalteparin OR enoxaparin OR nadroparin OR tinzaparin

Records retrieved: 450 studies

Total: 543, 507 records reviewed after 36 duplicates removed

Appendix 3: Summary of planned and ongoing studies

Treatment (per arm)	n	Severity at enrollment	Sponsor/Funder	Reg. number	Full text link
(1) Heparin vs (2) Standard of care	462	Moderate/severe	St. Michael's Hospital, Toronto	NCT04362085	https://clinicaltrials.gov/show/NCT04362085
(1) Heparin vs (2) Standard of care	172	Critical	St Vincents Hospital Melbourne	ACTRN12620000517976	https://anzctr.org.au/ACTRN12620000517976.aspx
(1) Heparin vs (2) Heparin	550	Moderate/severe/critical	CHRU de Nancy	EUCTR2020-001709-21-FR	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001709-21
(1) Heparin vs (2) Standard of care	3000	Mild/moderate	University of Manitoba	NCT04372589	https://clinicaltrials.gov/show/NCT04372589
(1) Heparin vs (2) Enoxaparin	602	Moderate/severe	Central Hospital, Nancy, France	NCT04373707	https://clinicaltrials.gov/show/NCT04373707
(1) Heparin vs (2) Heparin vs (3) Heparin	30	Severe/critical	Faculdade de Medicina de Ribeirâ—Žo Preto - Ribeirâ—Žo Preto, SP, Brazil	RBR-949z6v	http://www.ensaiosclinicos.gov.br/rg/RBR-949z6v/
(1) Heparin vs (2) Placebo	50	Critical	Frederick Health	NCT04397510	https://clinicaltrials.gov/show/NCT04397510
(1) Heparin vs (2) Heparin	186	Critical	Weill Medical College of Cornell University	NCT04406389	https://clinicaltrials.gov/show/NCT04406389
(1) Unfractioned heparin + enoxaparin vs (2) Unfractioned heparin + enoxaparin vs (3) Clopidogrel + unfractioned heparin + enoxaparin vs (4) Clopidogrel + unfractioned heparin + enoxaparin	750	Critical	The TIMI Study Group	NCT04409834	https://clinicaltrials.gov/show/NCT04409834
(1) Low molecular weight heparin (LMWH) vs (2) Methylprednisolone + heparin vs (3) Methylprednisolone + low molecular weight heparin (LMWH)	200	Critical	AZIENDA OSPEDALIERO-UNIVERSITARIA POLICLINICO DI MODENA	EUCTR2020-001921-30-IT	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001921-30/IT
(1) Unfractioned heparin vs (2) Standard of care vs (3) Tissue Plasminogen Activator	15	Critical	Tabriz University of Medical Sciences	IRCT20200515047456N1	http://en.irct.ir/trial/48929
(1) Heparin vs (2) Standard of care	100	Mild/moderate	Dr Tarek Ismail	PACTR202007606032743	https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=12158
(1) Low molecular weight heparin (LMWH) vs (2) Placebo	160	Moderate	Rujin Hospital; Shanghai Jiao Tong University School of Medicine	ChiCTR2000034796	http://www.chictr.org.cn/showproj.aspx?proj=55775
(1) Heparin vs (2) Methylprednisolone vs (3) Methylprednisolone + heparin vs (4) Standard of care	268	Severe	D'Or Institute for Research and Education	NCT04485429	https://clinicaltrials.gov/show/NCT04485429
(1) Enoxaparin OR unfractionated heparin vs (2) Enoxaparin OR unfractionated heparin vs (3) Atorvastatin vs (4) Placebo	410	Critical	Rajaie Cardiovascular Medical and Research Center	NCT04486508	https://clinicaltrials.gov/show/NCT04486508
(1) Unfractionated Heparin vs (2) Standard of care	90	No restriction on type of patients	University of Sao Paulo General Hospital	NCT04487990	https://clinicaltrials.gov/show/NCT04487990
(1) Heparin vs (2) Heparin	2000	Mild	Matthew Neal MD	NCT04505774	https://clinicaltrials.gov/show/NCT04505774
(1) Enoxaparin vs (2) Enoxaparin	130	Mild	Hospital Regional de Alta especialidad de Ixtapaluca	NCT04508439	https://clinicaltrials.gov/show/NCT04508439
(1) Heparin vs (2) Standard of care	40	Severe/critical	University College Hospital Galway	NCT04511923	https://clinicaltrials.gov/show/NCT04511923
(1) Enoxaparin vs (2) Methylprednisolone + enoxaparin vs (3) Methylprednisolone + unfractionated heparin	210	Critical	Massimo Girardis	NCT04528888	https://clinicaltrials.gov/show/NCT04528888
(1) Enoxaparin vs (2) Enoxaparin + heparin	200	Moderate	Clinica San Camilo, Argentina	NCT04530578	https://clinicaltrials.gov/show/NCT04530578
(1) Unfractioned heparin OR Low molecular weight heparin (LMWH) vs (2) Hydroxychloroquine vs (3) Hydroxychloroquine + lopinavir + ritonavir vs (4) Oseltamivir vs (5) Lopinavir + ritonavir vs (6) Interferon beta-1a vs (7)	1000	No restriction on type of patients	University Medical Center Utrecht	NCT02735707	https://clinicaltrials.gov/ct2/show/NCT02735707#contacts

Convalescent plasma treatment vs (8) Simvastatin vs (9) Anakinra vs (10) Tocilizumab vs (11) Sarilumab vs (12) Hydrocortisone vs (13) Vitamin C vs (14) Ceftriaxone + macrolide vs (15) Levofloxacin OR Moxifloxacin vs (16) Piperacillin-tazobactam + macrolide vs (17) Ceftaroline + macrolide vs (18) Amoxicillin-clavulanate + macrolide vs (19) Standard of care					
(1) Edoxaban vs (2) Edoxaban + low molecular weight heparin (LMWH) vs (3) Standard of care	172	No restriction on type of patients	Universitâ—Žtsklinikum Hamburg-Eppendorf	NCT04542408	https://clinicaltrials.gov/show/NCT04542408
(1) Nebulised unfractionated heparin (UFH) vs (2) Placebo	202	Critical	Australian National University	NCT04545541	https://clinicaltrials.gov/show/NCT04545541
(1) Low molecular weight heparin (LMWH) vs (2) Low molecular weight heparin (LMWH)	50	Moderate/severe/critical	Ain Shams University	NCT04584580	https://clinicaltrials.gov/show/NCT04584580
(1) Heparin vs (2) Standard of care	40	Critical	NUIG	EUCTR2020-003349-12-IE	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-003349-12/IE
(1) Heparin vs (2) Heparin vs (3) Heparin + tocilizumab vs (4) Heparin + tocilizumab	308	Moderate/severe/critical	University of Sao Paulo	NCT04600141	https://clinicaltrials.gov/show/NCT04600141
(1) Unfractionated heparin vs (2) Standard of care	656	Moderate/severe	Australian National University	NCT04635241	https://clinicaltrials.gov/show/NCT04635241
(1) Heparin vs (2) Dalteparin vs (3) enoxaparin sodium	150	Moderate/severe/critical	CONSORZIO FUTURO IN RICERCA	EUCTR2020-004285-19-IT	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-004285-19/IT
(1) Heparin vs (2) Placebo	50	Moderate/severe	Frederick Health	NCT04723563	https://clinicaltrials.gov/show/NCT04723563
(1) Nebulised unfractionated heparin (UFH) vs (2) Standard of care	100	Moderate/severe	Galeno Desenvolvimento de Pesquisas Clâ—Žnicas Ltda	RBR-8r9hy8f	http://ensaiosclinicos.gov.br/rg/RBR-8r9hy8f
(1) Heparin vs (2) Placebo	50	Moderate/severe	UPECLIN HC FM Botucatu Unesp	NCT04743011	https://clinicaltrials.gov/show/NCT04743011
(1) High molecular weight heparin (HMWH) vs (2) Placebo	40	Moderate	Faculdade de Medicina de Botucatu - UNESP	RBR-7y8j2bs	http://ensaiosclinicos.gov.br/rg/RBR-7y8j2bs
(1) Heparin vs (2) Placebo	40	Critical	University of Kentucky	NCT04842292	https://clinicaltrials.gov/show/NCT04842292

Appendix 4: Evidence to decision framework

Note: The evidence to decision framework was completed following the adolopment of the American Society of Hematology's Guidelines,– refer to the attached addendum for the completed online GRADEpro templates.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** **Intermediate dosing** Large [ ] Moderate [ ] Small [x] None [ ] Uncertain [ ] **Therapeutic dosing** Large [ ] Moderate [x] Small [ ] None [ ] Uncertain [ ]	**Intermediate dosing** *Severely ill COVID-19 confirmed hospitalized patients:* There may be little or no difference to the outcomes death, and there is substantial uncertainty regarding the effect of higher dosing on arterial or venous thrombosis and major bleeding or serious adverse events. **Therapeutic dosing** *Mixed hospitalized population:* There may be little or no difference in mortality or the WHO progression score to level 7 or above between those on intermediate compared to standard dose prophylactic anticoagulation. There may be fewer major thromboembolic events and increased major bleeding events.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **Intermediate dosing** Large [ ] Moderate [ ] Small [x] None [ ] Uncertain [ ] **Therapeutic dosing** Large [ ] Moderate [x] Small [ ] None [ ] Uncertain [ ]	**Intermediate dosing** *Severely ill COVID-19 confirmed hospitalized patients:* as above. **Therapeutic dosing** *Mild/ moderate and severely ill:* There may be more major bleeding in the therapeutic dosing group.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [X] Intervention = Control *or* Uncertain [ ]	**Intermediate dosing** Favours control, as evidence remains uncertain for severely/ critically ill. **Therapeutic dosing** Favours control, as benefits and harms may be balanced.
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [x] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Very low (based on lowest certainty for critical outcomes) – single trial.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Enoxaparin and unfractionated heparin are medicines listed on the National EML. However, laboratory test to measure factor Xa is inaccessible.
RESOURCE USE	**How large are the resource requirements?** More intensive [X] Less intensive [ ] Uncertain [ ]	Price of medicines/day: **Medicine** | **Tender price** | **Price - SEP** Enoxaparin, SC, 40 mg daily | R41.39* | R91.49** Unfractionated heparin, SC, 5000u 12 hourly | R8.28* | R16.28** *Contract circular RT297-2019 [Accessed 01/08/2020] - Heparin Sodium Fresenius 5000iu/5ml = R45.70 ** SEP database, excluding dispensing fees, March 2020 https://mpr.code4sa.org/ Bio-Heparin Sodium Fresenius 5000iu/ml = R16.28 **Additional resources:** n/a

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: ☐ Major: x Uncertain: ☐ **Is the option acceptable to key stakeholders?** Yes: ☐ No: ☐ Uncertain: x	*Patients:* No specific research surveying patients' value of this therapeutic agent is currently available, and NEMLC Subcommittee judged this as major uncertainty. *Healthcare workers:* Currently therapeutic doses of heparin for VTE prophylaxis are used in clinical practice for critically ill patients, based on local experience. Acceptability uncertain and may vary by setting.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	19 June 2020	RW, SM, KC	Recommend against using therapeutic doses of heparin for VTE prophylaxis for hospitalised COVID-19 patients; as currently there is insufficient evidence for routine use - consider in context of clinical trial setting.
Second	3 September 2020	RW, SM, KC	Recommend against using therapeutic doses of heparin for VTE prophylaxis for hospitalised COVID-19 patients; as currently there is insufficient evidence for routine use - consider in context of clinical trial setting.
Third	30 July 2021	TK, SM, RW, KC	Recommend against using therapeutic or intermediate doses of heparin for VTE prophylaxis for hospitalised COVID-19 patients; as the balance of benefits and harms supports the use of prophylactic doses.

ADDENDUM:
The completed online GRADEpro templates following the adolpment of the updated American Society of Hematology's Guidelines.

QUESTION ONE

Should anticoagulants at intermediate-intensity vs. prophylactic-intensity be used for patients with COVID-19 related critical illness who do not have suspected or confirmed VTE?	
POPULATION:	Patients with COVID-19 related critical illness who do not have suspected or confirmed VTE.
INTERVENTION:	anticoagulants at intermediate-intensity
COMPARISON:	prophylactic-intensity
MAIN OUTCOMES:	Mortality; Pulmonary embolism (follow-up: range 14 days to 20 days); Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT) (follow up: range 14 days to 20 days); Venous thromboembolism (follow-up: range 18 days to 28 days; assessed with: DVT or PE); Major bleeding (follow-up: mean 16 days); Multiple Organ Failure (follow up: mean 14 days; assessed with: Requirement for Renal replacement therapy) 0 t; Ischemic stroke (severe) (assessed with: any ischemic stroke); Intracranial hemorrhage; Invasive ventilation (follow-up: any duration); Limb amputation; ICU hospitalization; ST-elevation myocardial infarction (follow-up: mean 18 days).
SETTING:	Inpatient
PERSPECTIVE:	Population
BACKGROUND:	Patients hospitalized with COVID-19 related acute illness may develop hemostatic abnormalities and hypercoagulability. Early studies demonstrated high rates of venous thrombotic complications. Furthermore, COVID-19 may be associated with arterial thrombotic complications and microvascular thrombosis, particularly in the lungs. The extent to which hypercoagulability contributes to respiratory failure and multiorgan failure remains unclear. Early reports have suggested that patients with COVID-19 related acute illness have improved clinical outcomes with anticoagulant prophylaxis. However, the optimal intensity of anticoagulation and its effect on clinical outcomes is uncertain.
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Angchaisuksiri, Blair, Cuker, Dane, Davila, DeSancho, Diuguid, Griffin, Kahn, Klok, Lee, Mustafa, Neumann, A. Pai, M. Pai, Righini, Sanfilippo, Schünemann, Siegal, Skara, Touri, Tseng. No panel members were recused.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Coronavirus disease 2019 (COVID-19) infection is associated with venous thromboembolism (VTE), coupled with a poor prognosis (Loo et al., 2021; Malas et al., 2020; Tang et al., 2020). In South Africa COVID-19 adds to an already high prevalence of infectious diseases, including TB and HIV which both also increase the risk for VTE (Crum-Cianflone et al., 2008; Dentan et al., 2014). Due to the dearth of clinical trial data, there is no systematic and integrated approach to COVID-19-related VTE prevention in hospitalized COVID-19 patients (Ali & Spinler, 2021). In particular for ill and critically ill patients, there has been uncertainty on questions around timing and dosing of prophylactic anticoagulation. One of the tertiary hospitals in South Africa reports that all their inpatients with suspected or confirmed COVID-19 pneumonia receive VTE prophylaxis unless there is a contraindication (Mendelson et al., 2020). The use of low-molecular-weight heparin (LMWH) is preferred to unfractionated heparin because of its predictable pharmacokinetics and limited monitoring requirements (Leentjens et al., 2017). Despite standard heparin prophylaxis, however, the hospital reported an observation of VTE events. In 2020, they described a change in practice towards the provision of what is defined as enhanced or intermediate-dose enoxaparin prophylaxis, for patients with hypoxic pneumonia. This new strategy is based on expert opinion and is noncompliant with the current national guidance which recommends the use of standard-dose heparin prophylaxis in COVID-19 patients (Mendelson et al., 2020). This guidance is consistent with international guidance, which advises the use of prophylactic doses of heparin in COVID-19 patients. The new practice is done to overcome the anticipated heparin resistance in COVID-19 patients, due to increased circulating fibrinogen, factor VII and von Willebrand factor levels. Other institutions within the country also postulate that higher doses of LMWH are necessary due to high fibrinogen and high FVIII levels (Wessels, 2020). For critically ill COVID-19 patients in ICU, especially when inotropic support is required, higher LMWH doses are needed to achieve expected anti-Factor X activity (antiFXa) levels due to decreased subcutaneous absorption and augmented renal clearance. It is believed that the higher dose enoxaparin might also ensure better protection for obese patients who may be underdosed because of failure to do accurate weight-based dosing. There has been evidence from cohort studies of increased bleeding risk with high doses of heparin (Godier et al., 2021; Musoke et al., 2020). Therefore, the non- standard-dose heparin prophylaxis has been implemented with caution in patients above 70 years and those who have other bleeding risk factors (Mendelson et al., 2020). There is emerging trial evidence for determining appropriate heparin dosing in COVID-19 patients which is the purpose of the review. **References** • Ali, M. A. M., & Spinler, S. A. (2021). COVID-19 and thrombosis: From bench to bedside. *Trends in Cardiovascular Medicine*, *31*(3), 143–160. https://doi.org/10.1016/j.tcm.2020.12.004 • Crum-Cianflone, N. F., Weekes, J., & Bavaro, M. (2008). Review: Thromboses among HIV-infected patients during the highly active antiretroviral therapy era. *AIDS Patient Care and STDs*, *22*(10), 771–778. https://doi.org/10.1089/apc.2008.0010 • Dentan, C., Epaulard, O., Seynaeve, D., Genty, C., & Bosson, J. L. (2014). Active tuberculosis and venous thromboembolism: Association according to international classification of diseases, ninth revision hospital discharge diagnosis codes. *Clinical Infectious Diseases*, *58*(4), 495–501. https://doi.org/10.1093/cid/cit780 • Godier, A., Clausse, D., Meslin, S., Bazine, M., Lang, E., Huche, F., Cholley, B., & Hamada, S. R. (2021). Major bleeding complications in critically ill patients with COVID-19 pneumonia. *Journal of Thrombosis and Thrombolysis*, 3–6. https://doi.org/10.1007/s11239-021-02403-9 • Leentjens, J., Peters, M., Esselink, A. C., Smulders, Y., & Kramers, C. (2017). Initial anticoagulation in patients with pulmonary embolism: thrombolysis, unfractionated heparin, LMWH, fondaparinux, or DOACs? *British Journal of Clinical Pharmacology*, *83*(11), 2356–2366. https://doi.org/10.1111/bcp.13340 • Loo, J., Spittle, D. A., & Newnham, M. (2021). COVID-19, immunothrombosis and venous thromboembolism: Biological mechanisms. *Thorax*, *76*(4), 412–420.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

https://doi.org/10.1136/thoraxjnl-2020-216243

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Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	Major bleeding undesirable

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	*See Appendix 1*	Indirect evidence of increasing bleeding when doses increased. Current evidence of undesirable effects uncertain due to low event rates.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Mortality was moderate certainty, and SAEs were low certainty, but the remaining critical outcomes were very low certainty. Based on the lowest certainty for the critical outcomes, the overall certainty is very low.	Add considerations made be the adoloping panel, including the justification for any change in judgment

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Systematic review in patients about values and preferences related to the importance that patients place on health outcomes (e.g., bleeding, having a deep venous thrombosis). This is not in the context of COVID-19. The review identified 14 quantitative studies (2465 participants) describing the relative importance of VTE-related health states in a widely diverse population of patients, showing overall small to important impact on patients' lives (certainty of the evidence from low to moderate). Additionally, evidence from 34 quantitative studies (6424 participants) and 15 qualitative studies (570 participants) revealed that patients put higher value on VTE risk reduction than on the potential harms of the treatment (certainty of evidence from low to moderate). The observed variability in health state values may be a result of differences in the approaches used to elicit them and the diversity of included populations rather than true variability in values. This finding highlights the necessity to explore the variability induced by different approaches to ascertain values.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Example: 'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or 'additional global evidence indentified: xxx'.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	A comparison of the direct medicine prices, showed a two to threefold incremental cost if therapeutic or intermediate-intensity dosing was used. While the total medicine cost of the intervention would be higher, this would possibly be negligible compared to the total costs of providing critical care to these patients. Of note is that doses are modelled on a 70kg adult; and that the lack of a concentrated heparin formulation (i.e. 25 000iu) on the South African market only allows the more expensive option of enoxaparin for therapeutic of intermediate-dose anticoagulation. Enoxaparin Dosing regimens • prophylactic (40mg daily) • intermediate (0.5 mg/kg or 40mg BD) • therapeutic (1mg/kg BD) **Medicine acquisition costs:** Prophylactic anticoagulation • Enoxaparin, SC, 40mg daily (LMWH example of class) **R1608.30** • Unfractionated heparin, SC, 5000 iu 12 hourly **R108.17** Therapeutic anticoagulation • Enoxaparin, SC, 1.5mg/kg daily (LMWH example of class) **R4049.40** • Enoxaparin, SC, 1mg/kg 12 houry (LMWH example of class) **R4469.7** **Other resource requirements:** - are routine tests needed? e.g. anti factor Xa - add costs (NHLS) **R 531** **References:** Contact circular HP06-2021SVP http://www.health.gov.za/tenders/ Western Cape DoH buy-out prices (communication on file)	Panel noted these are public sector prices. Testing not feasible and not included in consideration.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Example: 'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or 'additional global evidence indentified: xxx'.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No additional research evidence reported.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No additional research reported.	Widely available

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence reported	The acceptability of the intervention to various stakeholders (patients, healthcare providers, institutions, etc.) was considered.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Thromboprophylaxis is already part of critical care of medical patients.	Testing not accessible

SUMMARY OF JUDGEMENTS

CRITERIA	ORIGINAL	IMPORTANCE FOR DECISION	ADOLOPMENT	IMPORTANCE FOR DECISION
PROBLEM			Yes	
DESIRABLE EFFECTS			Trivial	
UNDESIRABLE EFFECTS			Don't know	
CERTAINTY OF EVIDENCE			Very low	
VALUES			Possibly important uncertainty or variability	
BALANCE OF EFFECTS			Probably favors the comparison	
RESOURCES REQUIRED			Moderate costs	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES			No included studies	
COST EFFECTIVENESS			No included studies	
EQUITY			Probably no impact	
ACCEPTABILITY			Probably yes	
FEASIBILITY			Yes	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The NEMLC sub-committee suggest to use current standard prophylactic doses rather than intermediate doing anticoagulation.
Rationale: lack of clear benefit, possible harm, increased costs, inability to access testing.

Justification

Overall justification
Detailed justification
Balance of effects
While there was a suggestion of mortality benefit and reduction in VTE with intermediate-intensity or therapeutic-intensity anticoagulation, this evidence was of very low certainty. There was less uncertainty in the potential undesirable effects of intermediate-intensity or therapeutic-intensity anticoagulation in increasing the risk of major bleeding complications. Moreover, the panel considered that there was higher quality indirect evidence from non-COVID-19 critically ill patients for a dose-dependent increase in the risk of major bleeding with anticoagulation, although the magnitude of this effect was uncertain in the COVID-19 population. Given that there was very low certainty for benefit to offset the moderate risk of major bleeding complications, the usual practice of prophylactic-intensity anticoagulation in critically ill non-COVID-19 patients was suggested. The panel however acknowledged the potential for benefit, and noted that an individualized decision is important for each patient based on an assessment of thrombotic and bleeding risk. The panel emphasized that there is an urgent need for more high-quality prospective studies and randomized controlled trials examining the effect of differing anticoagulation intensities.

Subgroup considerations

For patients with extremes of body weight or renal impairment, dose adjustment of prophylactic-intensity anticoagulation may be appropriate.

Implementation considerations

Risk assessment models for assessing thrombosis and bleeding risk in non-COVID-19 hospitalized patients have been developed. However, these tools have not been validated in patients hospitalized with COVID-19.
References:
1. Barbar S, Noventa F, Rossetto V, et al. A risk assssment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost* 2010; 8: 2450-2457.
2. Spyropoulos AC, Anderson FA Jr, Fitzgerald G, et al. IMPROVE Investigators. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest* 2011; 140: 706-714.
3. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest* 2011; 139: 69-79.

Monitoring and evaluation

Patients receiving prophylactic-intensity, intermediate-intensity, or therapeutic-intensity anticoagulation therapy require regular reassessment of thrombotic and bleeding risk. It is important to frequently assess and optimize factors that affect the safety of anticoagulation therapy (e.g., renal function, thrombocytopenia, blood pressure control, minimizing concomitant antiplatelet therapy). Frequent clinical assessments for signs and symptoms of thromboembolism and bleeding are also necessary in critically ill patients.

The panel did not specifically address the use of anticoagulant monitoring with anti-Xa levels, or the use of screening lower extremity ultrasonography in asymptomatic patients. However, these measures are not routinely recommended for monitoring critically ill patients receiving anticoagulation therapy.

References:
1. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv* 2018; 2(22): 3257-3291.

Research priorities

- Studies assessing baseline VTE risk in critically ill patients on prophylactic-intensity anticoagulation therapy.
- Randomized controlled trials comparing anticoagulation at differing intensities (prophylactic vs. intermediate vs. therapeutic).
- Studies examining the impact of non-anticoagulant interventions (e.g., anti-complement therapy, corticosteroids, antiviral therapies, anticytokine therapies, antiplatelet therapies, monoclonal antibody therapy, convalescent plasma) on thrombotic risk.
- Development or validation of risk assessment models for thrombosis and bleeding in patients with COVID-19 related critical illness.
- Studies examining the impacts of anticoagulant therapy on thrombosis and bleeding outcomes in patients of differing race/ethnicity.
- Studies comparing mortality, thrombosis, bleeding, and functional outcomes with different available anticoagulant agents and intensities.

APPENDICES

Appendix 1

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without anticoagulants at intermediate-intensity	With anticoagulants at intermediate-intensity	Difference		
Death № of participants: 774 (2 RCTs)	**RR 0.99** (0.82 to 1.19)	Study population			⨁⨁⨁◯ MODERATE[a]	Anticoagulants at intermediate-intensity probably results in little to no difference in death.
		34.9%	34.5% (28.6 to 41.5)	0.3% fewer (6.3 fewer to 6.6 more)		
Arterial thrombosis № of participants: 176 (1 RCT)	**RR 2.50** (0.50 to 12.54)	Study population			⨁◯◯◯ VERY LOW[a,b]	The evidence is very uncertain about the effect of anticoagulants at intermediate-intensity on arterial thrombosis.
		2.3%	5.7% (1.1 to 28.5)	3.4% more (1.1 fewer to 26.2 more)		
Venous thrombosis № of participants: 738 (2 RCTs)	**RR 1.02** (0.50 to 2.08)	Study population			⨁◯◯◯ VERY LOW[a,b]	The evidence is very uncertain about the effect of anticoagulants at intermediate-intensity on venous thrombosis.
		4.3%	4.4% (2.1 to 8.9)	0.1% more (2.1 fewer to 4.6 more)		
Major bleeding № of participants: 738 (2 RCTs)	**RR 1.53** (0.55 to 4.30)	Study population			⨁◯◯◯ VERY LOW[a,b]	Anticoagulants at intermediate-intensity may increase major bleeding but the evidence is very uncertain.
		1.6%	2.5% (0.9 to 6.9)	0.9% more (0.7 fewer to 5.3 more)		
Duration of hospitalization; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation - not reported	-	-	-	undefined	-	
Serious adverse events № of participants: 598 (1 RCT)	**RR 1.01** (0.85 to 1.21)	Study population			⨁⨁◯◯ LOW[a,c]	Anticoagulants at intermediate-intensity may result in little to no difference in serious adverse events.
		45.5%	45.9% (38.7 to 55)	0.5% more (6.8 fewer to 9.6 more)		

a. Risk of bias downgraded by 1 level: some concern regarding deviation from intended intervention, missing data and selection of reported results.
b. Very small number of events and patients included in the intervention studies, lowering the certainty by two levels for imprecision
c. Imprecision downgraded by 1 level: due to small sample size.

QUESTION TWO

Should anticoagulants at therapeutic-intensity vs. prophylactic-intensity be used for patients hospitalised with COVID-19 who do not have suspected or confirmed VTE?	
POPULATION:	Patients with COVID-19 related critical illness who do not have suspected or confirmed VTE.
INTERVENTION:	anticoagulants at therapeutic-intensity
COMPARISON:	prophylactic-intensity
MAIN OUTCOMES:	Mortality; Pulmonary embolism (follow-up: range 14 days to 20 days); Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT) (follow up: range 14 days to 20 days); Venous thromboembolism (follow-up: range 18 days to 28 days; assessed with: DVT or PE); Major bleeding (follow-up: mean 16 days); Multiple Organ Failure (follow up: mean 14 days; assessed with: Requirement for Renal replacement therapy) 0 t; Ischemic stroke (severe) (assessed with: any ischemic stroke); Intracranial hemorrhage; Invasive ventilation (follow-up: any duration); Limb amputation; ICU hospitalization; ST-elevation myocardial infarction (follow-up: mean 18 days).
SETTING:	Inpatient
PERSPECTIVE:	Population
BACKGROUND:	Patients hospitalized with COVID-19 related acute illness may develop hemostatic abnormalities and hypercoagulability. Early studies demonstrated high rates of venous thrombotic complications. Furthermore, COVID-19 may be associated with arterial thrombotic complications and microvascular thrombosis, particularly in the lungs. The extent to which hypercoagulability contributes to respiratory failure and multiorgan failure remains unclear. Early reports have suggested that patients with COVID-19 related acute illness have improved clinical outcomes with anticoagulant prophylaxis. However, the optimal intensity of anticoagulation and its effect on clinical outcomes is uncertain.
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Angchaisuksiri, Blair, Cuker, Dane, Davila, DeSancho, Diuguid, Griffin, Kahn, Klok, Lee, Mustafa, Neumann, A. Pai, M. Pai, Righini, Sanfilippo, Schünemann, Siegal, Skara, Touri, Tseng. No panel members were recused.

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without anticoagulants at therapeutic-intensity	With anticoagulants at therapeutic-intensity	Difference		
Death № of participants: 1840 (3 RCTs)	**RR 1.11** (0.85 to 1.45)	Study population			⨁⨁◯◯ LOW[a,b]	The evidence suggests that anticoagulants at therapeutic-intensity results in little to no difference in death.
		23.1%	**25.7%** (19.7 to 33.6)	**2.5% more** (3.5 fewer to 10.4 more)		

Add considerations made be the adoloping panel, including the justification for any change in judgment.

Major thromboembolic events № of participants: 3193 (3 RCTs)	**RR 0.56** (0.40 to 0.80)	Study population			⨁⨁◯◯ LOW[a,b]	Anticoagulants at therapeutic-intensity may reduce major thromboembolic events.
		5.4%	**3.0%** (2.1 to 4.3)	**2.4% fewer** (3.2 fewer to 1.1 fewer)		
WHO Progression score 7 or above follow up: 28 days № of participants: 2860 (2 RCTs)	**RR 0.97** (0.75 to 1.26)	Study population			⨁⨁◯◯ LOW[a,b]	Anticoagulants at therapeutic-intensity may result in little to no difference in WHO Progression score 7 or above.
		11.5%	**11.1%** (8.6 to 14.5)	**0.3% fewer** (2.9 fewer to 3 more)		

a. Risk of bias downgraded by 1 level: some concern regarding deviation from intended intervention, missing data and selection of reported results.
b. Imprecision downgraded by 1 level: due to small sample size.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	

○ Large
● Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without anticoagulants at therapeutic-intensity	With anticoagulants at therapeutic-intensity	Difference		
Major bleeding № of participants: 3224 (3 RCTs)	**RR 1.66** (0.97 to 2.83)	Study population			⨁⨁◯◯ LOW[a,b]	Anticoagulants at therapeutic-intensity may increase major bleeding slightly.
		1.4%	**2.2%** (1.3 to 3.8)	**0.9% more** (0 fewer to 2.5 more)		
Duration of hospitalization; progression to ICU admission duration of ICU stay; duration of mechanical ventilation; serious adverse events - not reported	-	-	-	undefined	-	

a. Risk of bias downgraded by 1 level: some concern regarding deviation from intended intervention, missing data and selection of reported results.
b. Imprecision downgraded by 1 level: due to small sample size.

Add considerations made be the adoloping panel, including the justification for any change in judgment.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
● Very low ○ Low ○ Moderate ○ High ○ No included studies	All critical outcomes were rated as very low certainty of evidence.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Systematic review in patients about values and preferences related to the importance that patients place on health outcomes (eg, bleeding, having a deep venous thrombosis). This is not in the context of COVID-19. The review identified 14 quantitative studies (2465 participants) describing the relative importance of VTE-related health states in a widely diverse population of patients, showing overall small to important impact on patients' lives (certainty of the evidence from low to moderate). Additionally, evidence from 34 quantitative studies (6424 participants) and 15 qualitative studies (570 participants) revealed that patients put higher value on VTE risk reduction than on the potential harms of the treatment (certainty of evidence from low to moderate). The observed variability in health state values may be a result of differences in the approaches used to elicit them and the diversity of included populations rather than true variability in values. This finding highlights the necessity to explore the variability induced by different approaches to ascertain values.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified to address the impact on health equity.	As this treatment is already available, this is not considered to impact equity considerations.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Anticoagulation is already in use and would likely be accepytible for key stakeholders.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Adolopment	
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Thromboprophylaxis is being implemented in health facilities.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

SUMMARY OF JUDGEMENTS

CRITERIA	ORIGINAL	IMPORTANCE FOR DECISION	ADOLOPMENT	IMPORTANCE FOR DECISION
PROBLEM			Yes	
DESIRABLE EFFECTS			Moderate	
UNDESIRABLE EFFECTS			Moderate	
CERTAINTY OF EVIDENCE			Very low	
VALUES			Possibly important uncertainty or variability	
BALANCE OF EFFECTS			Does not favor either the intervention or the comparison	
RESOURCES REQUIRED			Moderate costs	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES			No included studies	
COST EFFECTIVENESS			No included studies	
EQUITY			Probably no impact	
ACCEPTABILITY			Probably yes	
FEASIBILITY			Probably yes	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The committee suggest to use standard prophylactic doses rather than therapeutic doses of anticoagulation for acutely and severely ill patients hospitalised with COVID-19.

Justification

Overall justification
Detailed justification
Balance of effects
While there was a suggestion of mortality benefit and reduction in VTE with intermediate-intensity or therapeutic-intensity anticoagulation, this evidence was of very low certainty. There was less uncertainty in the potential undesirable effects of intermediate-intensity or therapeutic-intensity anticoagulation in increasing the risk of major bleeding complications. Moreover, the panel considered that there was higher quality indirect evidence from non-COVID-19 critically ill patients for a dose-dependent increase in the risk of major bleeding with anticoagulation, although the magnitude of this effect was uncertain in the COVID-19 population. Given that there was very low certainty for benefit to offset the moderate risk of major bleeding complications, the usual practice of prophylactic-intensity anticoagulation in critically ill non-COVID-19 patients was suggested. The panel however acknowledged the potential for benefit, and noted that an individualized decision is important for each patient based on an assessment of thrombotic and bleeding risk. The panel emphasized that there is an urgent need for more high-quality prospective studies and randomized controlled trials examining the effect of differing anticoagulation intensities.

Subgroup considerations

For patients with extremes of body weight or renal impairment, dose adjustment of prophylactic-intensity anticoagulation may be appropriate.

The committee suggest to use standard prophylactic doses rather than therapeutic doses of anticoagulation for acutely and severely ill patients hospitalised with COVID-19.

Implementation considerations

Risk assessment models for assessing thrombosis and bleeding risk in non-COVID-19 hospitalized patients have been developed. However, these tools have not been validated in patients hospitalized with COVID-19.

References:

1. Barbar S, Noventa F, Rossetto V, et al. A risk assssment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost* 2010; 8: 2450-2457.
2. Spyropoulos AC, Anderson FA Jr, Fitzgerald G, et al. IMPROVE Investigators. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest* 2011; 140: 706-714.
3. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest* 2011; 139: 69-79.

Monitoring and evaluation

Patients receiving prophylactic-intensity, intermediate-intensity, or therapeutic-intensity anticoagulation therapy require regular reassessment of thrombotic and bleeding risk. It is important to frequently assess and optimize factors that affect the safety of anticoagulation therapy (e.g., renal function, thrombocytopenia, blood pressure control, minimizing concomitant antiplatelet therapy). Frequent clinical assessments for signs and symptoms of thromboembolism and bleeding are also necessary in critically ill patients.

The panel did not specifically address the use of anticoagulant monitoring with anti-Xa levels, or the use of screening lower extremity ultrasonography in asymptomatic patients. However, these measures are not routinely recommended for monitoring critically ill patients receiving anticoagulation therapy.

References:

1. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv* 2018; 2(22): 3257-3291.

Research priorities

- Studies assessing baseline VTE risk in critically ill patients on prophylactic-intensity anticoagulation therapy.
- Randomized controlled trials comparing anticoagulation at differing intensities (prophylactic vs. intermediate vs. therapeutic).
- Studies examining the impact of non-anticoagulant interventions (e.g., anti-complement therapy, corticosteroids, antiviral therapies, anticytokines, antiplatelets, monoclonal antibody therapy, convalescent plasma) on thrombotic risk.
- Development or validation of risk assessment models for thrombosis and bleeding in patients with COVID-19 related critical illness.
- Studies examining the impacts of anticoagulant therapy on thrombosis and bleeding outcomes in patients of differing race/ethnicity.
- Studies comparing mortality, thrombosis, bleeding, and functional outcomes with different available anticoagulant agents and intensities.